NUMBER 4

PAGE

OSCOPE
adareff 364
rmison 370
E RATS
Everitt 378
Everitt 382
IES IN
E. Kirk 388
N AND
Cohen 391
AFTER
Pincus 394
erauer 398
Grimes 401
404
ESSION
Orme 408
Fink 414
418
L SO-
422
427
Shock 445
Shock 469
481

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HISTOCHEMICAL AND DEGENERATIVE CHANGES IN THE ADRENAL CORTEX OF THE RAT WITH AGE*

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In a previous communication it was shown that the parenchymal cells of the adrenal gland underwent alterations which were related to advancing age (6). In conjunction with the process of cellular degeneration in the cortex, the lipids were seemingly reduced in quantity or absent in areas which were severely affected.

The general distribution of fat in the adrenal cortex of the rat was described by Jackson (5) and Watson (13). Van Dorp and Deane (12) found that the staining reactions for ketosteroids and for cholesterol were faint during the first few days after birth but became more intense with progressing age (up to 6 weeks). Studies by Tobin and Whitehead (11) revealed that the fat content in the inner half of the cortex varied with age in rats up to 1 year of age and that the distribution of cholesterol was the same as that of fat.

Previous studies of the adrenal lipids have not included rats more than 1 year of age, and it is the purpose of this investigation to observe the distribution of lipids and related materials in the adrenal gland of the rat at different age levels.

MATERIAL AND METHODS

The right adrenal of 60 albino male rats of the Wistar strain were studied. Group 1 consisted of 40 rats with the following distribution according to age: 10 rats, 14 to 25 days; 10 rats, 41 to 52 days; 10 rats, 90 to 100 days; 5 rats, 210 to 270 days; and 5 rats, 330 to 348 days. Group 2 consisted of 20 rats, 4 of which were 360 to 547 days and 16 of which were 600 to 900 days. The animals were killed by a blow on the head and the adrenals carefully removed to avoid crushing. The specimens were fixed in 10 per cent formalin containing 1 per cent calcium chloride, washed, and embedded in gelatin. The gelatin blocks were immersed in 10 per cent formalin containing 1 per cent calcium chloride and 1 per cent cadmium chloride and stored at about 2 C. for three days. Sections were cut at 15 μ and mounted on gelatin coated slides. Sections of each gland were (a) stained with Sudan black for fat, (b) treated by the Schultz method for cholesterol, and (c) treated with the Schiff reagent for plasmal. The technical procedures for staining as well as for fixation and embedding were the same as those employed by Yoffey and Baxter (14).

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RESULTS

Since the distribution and intensity of the Schultz-positive, Schiff-positive, and sudanophil materials were roughly the same, it will suffice to describe the results obtained with Sudan black and mention the specimens in which the distribution of the reactive materials for the respective stains were variant.

At all age levels the zona glomerulosa was quite irregular in its staining reaction. Occasionally it was the most heavily stained part of the cortex; frequently its staining was patchy, with some areas showing little or no stain while others were heavily stained. The marked variability in staining of the glomerulosa as compared with the remainder of the cortex was also observed by Yoffey and Baxter (14).

Group 1: 14- to 348-day-old rats

At 2 weeks, the cortex was divisible into three fat-containing zones, corresponding to the glomerular, fascicular, and rectricular zones. Another zone, termed the zone of compression by Mitchell (7) and the transitional zone by Van

Dorp and Deane (12), was observed in the majority of specimens of all age groups. This narrow zone, situated between the glomerulosa and the fasciculata, contained relatively little sudanophil material.

On the whole the staining intensity of the cortex of the 2 week specimen was light in comparison to that of older (100 day) specimens (compare figs. 1 and 2). The stain was usually denser in the outer half of the fasciculata than in the inner half and denser in the latter than in the reticularis. With progressing age the staining in the glomerulosa and fasciculata became more intense and seemingly reached a maximum at about 3 months (fig. 2).

The present observations concerning the variations in size of the inner zones with age are in agreement with those of Tobin and Whitehead (11). The reticularis was broadest at 14 days (breadth of reticularis/breadth of cortex-varied between one-half and two-thirds) and became progressively narrower with increasing age. Furthermore, at all age levels the size of the fasciculata varied inversely as the size of the reticularis. At 348 days the breadth of the reticularis was approximately one-third that of the cortex.

Some of the parenchymal cells within the inner half of the cortex contained yellow to brown pigment granules. The granules were rarely observed in specimens younger than 3 months, but became more abundant with increasing age.

Group 2: 360- to 900-day-old rats

The different portions of the glomerulosa in group 2 were even more variable in their straining reactions than the specimens in group 1. This variability in staining, coupled with the cellular changes which affected all the cortical zones, frequently obliterated all evidence of zonation. An estimation of the glomerular fat content among the various specimens is indicated in table 1, which shows that fat was absent in 1 animal and scanty in 10.

The zona reticularis was variable in size among the different specimens as well as within the different regions of the same specimen. The transition between the fasciculata and the reticularis was a gradual one, however; the breadth of the latter was estimated as being approximately one-third to one-fourth that of the cortex.

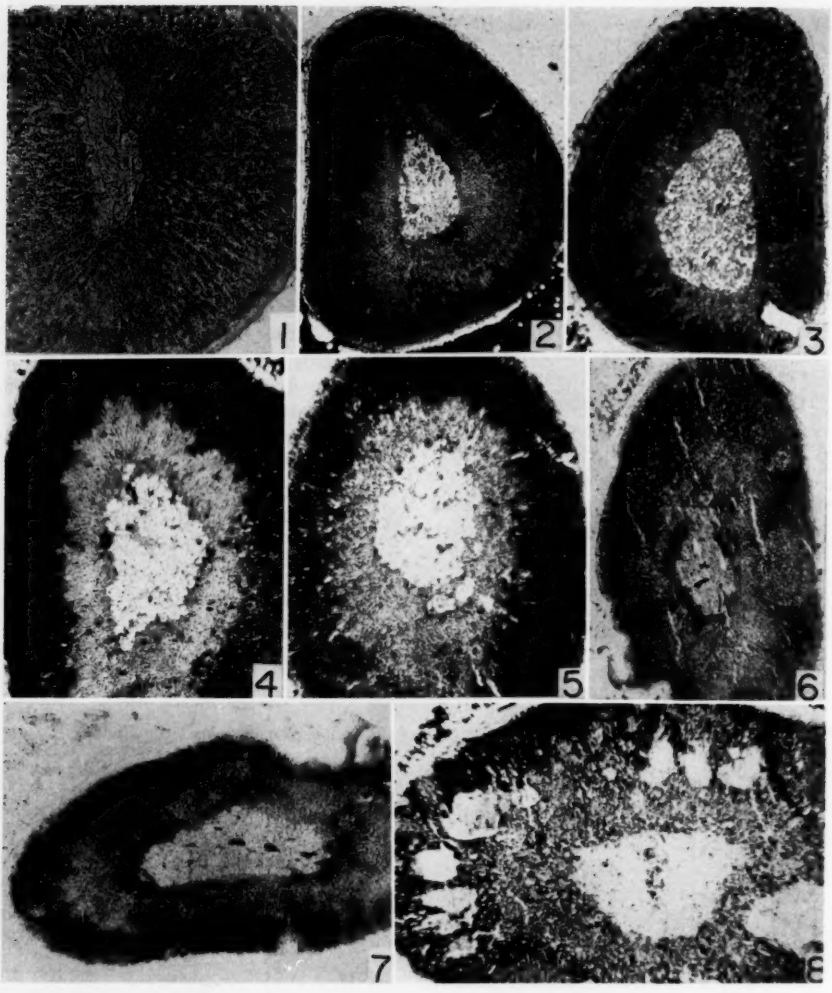
TABLE 1. RELATIVE AMOUNT OF SUDANOPHIL MATERIAL AND DEGENERATIVE CHANGES.

ANIMAL NO.	AGE IN DAYS	SUDANOPHIL DENSITY/1		CELLULAR DEGENERATION/2		NO. OF NODULES	BLOOD CHANNELS		PIGMENT DENSITY/3
		Glom.	Fasc.	Glom.	Fasc.		Cortex	Medulla	
1.	360–547	++++	++++	0	0	0	normal	normal	+
2.	360–547	++++	++++	0	0	0	normal	normal	+
3.	360–547	+++	++++	0	0	0	normal	normal	+
4.	360–547	++	+++	½	½	1	normal	normal	+
5.	900	+++	++++	0	0	0	normal	normal	+++
6.	780	+	++	½	½	1	normal	dilated	++
7.	780	+	++	½	½	1	normal	normal	+
8.	763	0	+	all	all	2	normal	dilated	+++
15.	720	+	+++	0	1/5	2	normal	normal	+++
18.	720	+++	++	0	¼	0	dilated	dilated	++
19.	900	+	+	½	½	2	dilated	normal	+++
20.	790	++	+++	1/5	1/5	1	normal	normal	+
21.	780	++	+++	0	0	0	normal	dilated	++
22a.	780	++++	++++	0	0	0	normal	dilated	+++
22b.	780	+	+++	½	½	0	normal	normal	+++
23.	790	+	+++	½	½	2	dilated	dilated	+++
25.	750	+	+++	0	0	0	normal	normal	++
47.	600	+	+++	0	0	1	normal	normal	+
53.	750	+	++	½	½	1	normal	dilated	+++
54.	750	+	+++	0	0	1	normal	normal	+++

/1 Estimate of relative amount of sudanophil material considering both distribution and density.

/2 Estimate of proportion of outer zones with evidence of extensive cellular degeneration.

/3 Rough estimate of relative amount of pigment granules (+ – scanty; ++ – moderate; +++ – abundant).



All figures on this plate are from adrenals fixed in formalin-calcium chloride, sectioned at 15 μ, and stained with Sudan black unless otherwise indicated.

1. From a 14-day-old rat showing light staining intensity of the cortex. X 50.

2. From a 100-day-old rat depicting a gradient in staining intensity. The glomerulosa is heavily stained in some regions and slightly in others. X 25.

3. From a 270-day-old specimen showing slightly stained glomerulosa. Note the relatively large vascular channel in the cortex. X 25.

4. From a 360-day-old specimen. The heavily stained glomerulosa serves to emphasize the transitional zone. X 25.

5. Animal No. 5, age, 900 days. Depicts normal staining intensity and distribution of lipids. X 25.

6. Animal No. 15, age, 720 days. Note extensive cellular degeneration and hyperplastic areas. X 20.

7. Section from same specimen as figure 6 (plasmal stain). X 20.

8. Animal No. 19, age, 900 days. Shows irregular distribution of sudanophil material and extensive vascularization of the cortex. X 25.

In 10 of the 20 specimens the cortex was normal in appearance and the distribution and density of the sudanophil material was much the same as that of younger specimens (compare figs. 3, 4 and 5). However, relatively large cortical areas in the remaining 10 specimens showed signs of cellular degeneration as well as subnormal amounts of sudanophil material. As stated previously, the Schultz-positive, Schiff-positive and sudanophil zones showed a rough parallelism. The zones affected by cellular degeneration, however, infrequently showed small amounts of sudanophil and Schultz-positive materials but gave a negative plasmal reaction. The relative amounts of sudanophil materials and a variety of degenerative changes affecting the various specimens, summarized in the table, will be discussed.

In 8 of the 10 specimens approximately half of the cortex was affected by cellular degeneration; the remaining 2 specimens were affected in lesser degree and in localized areas. The degenerative changes included the following:

1. The majority of cells in the necrotic zones in varying degrees were shrunken and their nuclear spaces compressed;

2. In many instances the normal arrangement of the cells was so distorted as a result of shrinkage that all semblance of zonation was obliterated;

3. Coincident with cellular shrinkage, the sudanophil granules were dark and opaque and frequently clumped or coalesced;

4. The staining results in the areas affected by advanced stages of cellular degeneration indicated the presence of little or no reactive materials (figs. 7 and 8);

5. Five specimens contained areas of fatty degeneration;

6. The degenerative phenomena were in some instances accompanied by adenoma-like nodules (figs. 7, 9, and 11).

The fatty degeneration most frequently occurred as relatively large areas in the zona fasciculata and less frequently in the zona reticularis (figs. 9 and 12). Cells which showed evidence of fatty degeneration were usually sudanophobic, although some were stained in varying degrees. Albert and Leblond (1) also reported that occasional cortical cells which showed signs of fatty degeneration gave a positive plasmal reaction; in this instance, they regarded a positive plasmal reaction as being indicative of passive storage of material rather than functional activity.

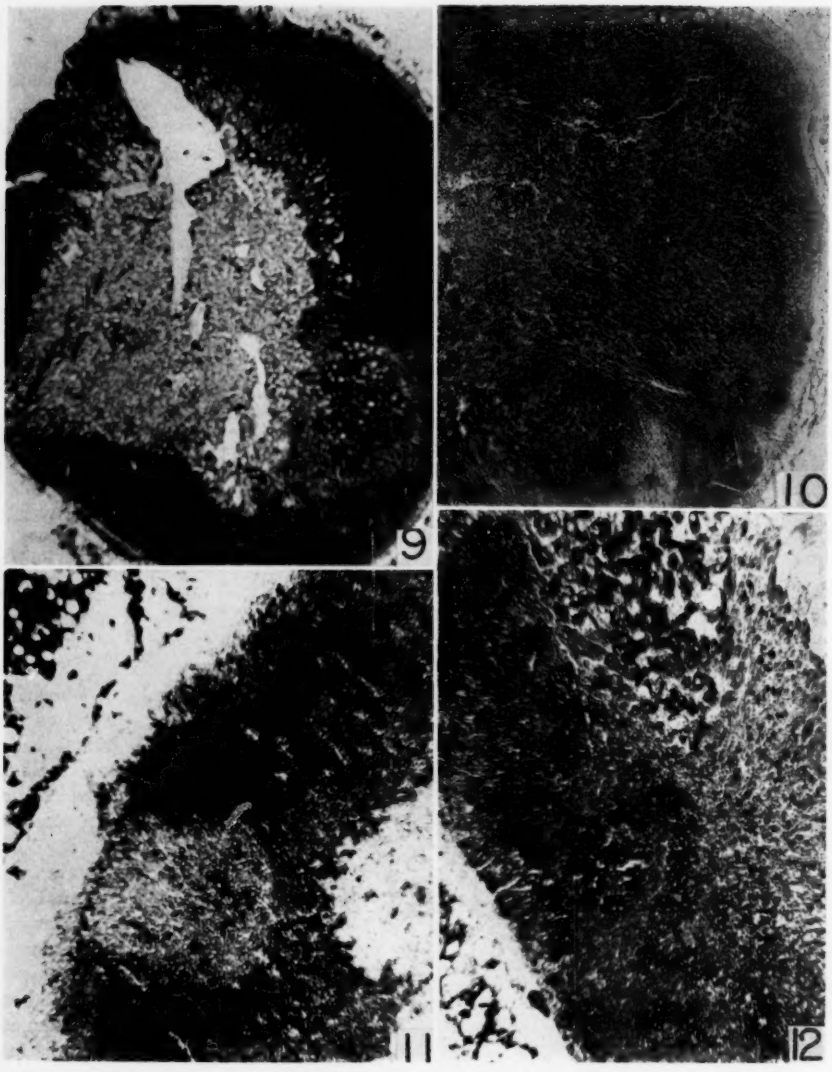
The nodules, referred to previously, were situated within the zona fasciculata and in some cases extended into the adjacent zones. Within the nodules there was a tendency to reproduce the normal cortical structure consisting of trabeculae. The latter, however, were distorted because of centrifugal growth, resulting in a whorled arrangement of the cell cords (fig. 10). The majority of the cells were shrunken and showed only a slight degree of sudanophilia; some of the cells so affected were obviously undergoing fatty degeneration.

The intracellular pigment granules also found in the inner cortical zones were more numerous than in the specimens of group 1. The adrenal glands in which the pigment granules were most abundant were those severely affected by cellular deterioration (figs. 6 and 12).

One of the 8 necrotic specimens also showed evidence of cortical atrophy, a large proportion of the cortex being reduced to a narrow rim (fig. 9). The staining intensity throughout the cortex indicated only traces of sudanophil material. The cells within the atrophic areas showed a succession of degenerative changes, and some were reduced to fragments; the reticular trabeculae were distorted and their cellular components heavily pigmented, while the zones in the outer portion of the rim were indistinguishable.

Table 1 shows that the vascular channels were unusually large in 8 specimens, 6 of which were among the specimens which showed maximum cellular degeneration. The enlarged vessels and increased vascularity in some specimens extended throughout the gland; in others only the cortex or the medulla was so affected (figs. 8 and 9). Cellular debris was sometimes observed within the dilated vessels which otherwise seemed normal.

A small mass of accessory cortical tissue was found in each of 3 specimens (numbers 3, 8, and 54). The first was intracapsular in its location and consisted of typical glomerular and fascicular zones. The second formed a continuum with the parenchyma at the pole of the principal gland; its shape was that of a hook and no particular zones could be discerned. This particular pole of the gland was not encapsulated. The accessory glandular growth of the third specimen was continuous with and ex-



All figures on this plate are from adrenals fixed in formalin-calcium chloride, sectioned at 15 μ, and stained with Sudan black unless otherwise indicated.

9. Animal No. 53, age, 750 days. Depicts cortical atrophy, hyperplastic nodules. The unstained spherical structures represent cells affected by fatty degeneration. X 28.

10. From a 780-day-old specimen depicting a hyperplastic area in which the cells are shrunken and show only traces of Schiff-positive material. Plasmal stain. X 57.

11. Animal No. 54, age 750 days. A sudanophobic area of hyperplasia within the relatively narrow cortex. X 70.

12. From a 750-day-old specimen. Note evidence of cellular degeneration throughout the cortex, including signet ring cells (fatty degeneration) and pigment granules in the reticularis. X 70.

ternal to the capsule of the principal gland. In each instance, the accessory cortical nodules showed a small degree of sudanophilia.

DISCUSSION

During the early aging process, two changes were observed: 1) a gradual decrease in the relative size of the reticularis coincident with a corresponding increase in the size of the fat-laden zone and 2) the fat-laden zone seemed to attain its maximum staining intensity at about 3 months.

Perhaps the most significant age changes were those observed in rats more than 1 year of age. In half the specimens a large proportion of the cells were so affected by the process of cellular degeneration that it would seem highly probable that their secretory capacity was either limited or nil. In sections of the mouse adrenal and sex glands, the staining intensity with fuchsin sulphurous acid increased until puberty, was maintained during sexual maturity, and subsequently decreased with increasing age (1). The decrease in staining which was associated with age was accompanied by cellular degeneration as well as an increase in amount of brownish "wear and tear" pigment, as indicated here for the rat. Working with old mice, Hooker and Pfeiffer (4) likewise observed pigment degeneration in the steroid-secreting cells of the testis as the content in bound aldehyde decreased and the secretory role was decreased or terminated.

Degenerative and atrophic changes in the adrenal cortex following hypophysectomy are revealing in so far as endocrine interrelationships are concerned. Ablation of the pituitary resulted in atrophic changes in the cortical cells consisting of shrinkage and partial disappearance of the cells in the zona fasciculata and the occurrence of numerous pycnotic and extruded nuclei in the zona reticularis (2, 8, 9). These results suggest that the functional state of the pituitary may be in some measure responsible for the degenerative changes in the inner cortical zones of old animals.

For obvious reasons, our knowledge concerning age changes in the adrenal gland of man is limited. Davis (3), however, reported that the cortex showed fibrosis and a decrease in number of parenchymal cells. Investigations by Solomon and Shock (10) indicated that in elderly men the ability of the adrenal cortex to secrete hormones of the 11-17-oxysteroid group under ACTH stimulus was not grossly impaired in senescence.

SUMMARY

The histologic distribution of fat and related materials in the adrenal cortex has been studied in 60 normal rats at various ages from 14 to 900 days.

In general distribution and intensity the Schultz-positive, Schiff-positive and sudanophil materials were the same.

The maximum staining intensity was attained at about 3 months of age; thereafter no significant changes were observed until the age of 1 year.

While the cortex in 10 of the 20 specimens 1 year of age and older was normal in appearance, the remaining 10 specimens were affected in varying degrees by degenerative changes.

On the basis of the observations presented, it would seem that the capacity to produce steroid hormones by the parenchymal cells of the adrenal cortex may be substantially decreased as a result of cellular degeneration.

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AGE FACTOR AND HIGH-FAT DIETS IN THE EVOLUTION OF OSTEOARTHRITIS IN MICE*

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In male mice of strain C57BL, feeding a high-fat diet through life increased the incidence and advanced the onset of degenerative joint disease as compared to conditions in controls fed a stock diet. The ultimate incidence of the joint disease was about the same, irrespective of the age at which the dietary regimen was instituted, although the lesions produced were of comparatively low grade in the oldest group of animals tested (6). In these studies, the induction period was the shorter, the older the animals at the beginning of the experiment. Therefore, the role of age in the susceptibility of the articular tissues to osteoarthritis warranted further investigation. For this purpose, a series of experiments were carried out in which mice were fed a high-fat diet for equal but limited periods of time at various ages.

MATERIAL AND METHODS

One hundred and forty-six male mice of the closely inbred strain C57BL raised in our laboratory were placed on a high-fat ration from (a) 1 to 5 months of age (49 mice); (b) 6 to 11 months of age (51 mice); and (c) 12 to 17 months of age (46 mice). Before and after the experimental periods, the animals received a stock diet of Purina Laboratory Chow, which contains 5 per cent fat. The high-fat diet, the composition of which has been previously described in detail (6), was prepared by grinding the laboratory Chow to a meal and adding 25 per cent lard (Swift's Silverleaf Brand). This diet is well tolerated by the animals. The rations were fed ad libitum with water available at all times. The mice were scheduled to be killed at the ages of 18 or 24 months. However, some animals had to be sacrificed prematurely because they were sick or dying (table 1). At necropsy, the knee joints, including the upper end of the tibia and the lower end of the femur, were removed as a whole, fixed and decalcified in Bouin's solution, and slides were prepared for microscopic examination.

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The findings obtained were compared with those observed previously in stock-fed animals and in mice fed the same high-fat diet through life from the ages of 1, 6, or 12 months on (6).

RESULTS

(a) Weights: The mice fed the high-fat diet for 5 months showed a temporary increase in weight, which usually was about 5 per cent but never exceeded 10 per cent. Mice fed the high-fat ration at the age of 12 to 17 months showed practically no gain in weight. After the mice had been returned to the stock diet, the weights became normal again and showed the decline that ordinarily occurs with advancing age.

(b) Life span: While feeding of the enriched diet through life shortened the life span, the limited exposure to the high-fat diet did not influence life expectancy adversely. These data have been reported elsewhere (7).

TABLE 1. INCIDENCE OF OSTEOARTHRITIS IN MICE OF THE VARIOUS EXPERIMENTAL GROUPS.

Experiment	Age Range (Months)	No.	Mean Age (Months)	Osteoarthritis (%)
High-fat diet 2–6 mo.	13–18	23	16.3	52.2
	13–32	49	20.6	59.2
High-fat diet 6–11 mo.	13–18	29	17.1	41.3
	13–33	51	18.2	47.0
High-fat diet 12–17 mo.	13–18	20	17.9	55.0
	13–29	46	21.3	41.3
Stock diet 2–30 mo.	13–18	34	16.8	32.4
	13–30	70	19.6	44.4
High-fat diet 2–22 mo.	13–18	51	16.3	68.6
	13–22	78	18.3	73.1
High-fat diet 6–24 mo.	13–18	19	17.9	52.6
	13–24	38	20.0	71.4
High-fat diet 12–24 mo.	13–18	15	17.7	60.0
	13–24	32	20.7	65.6

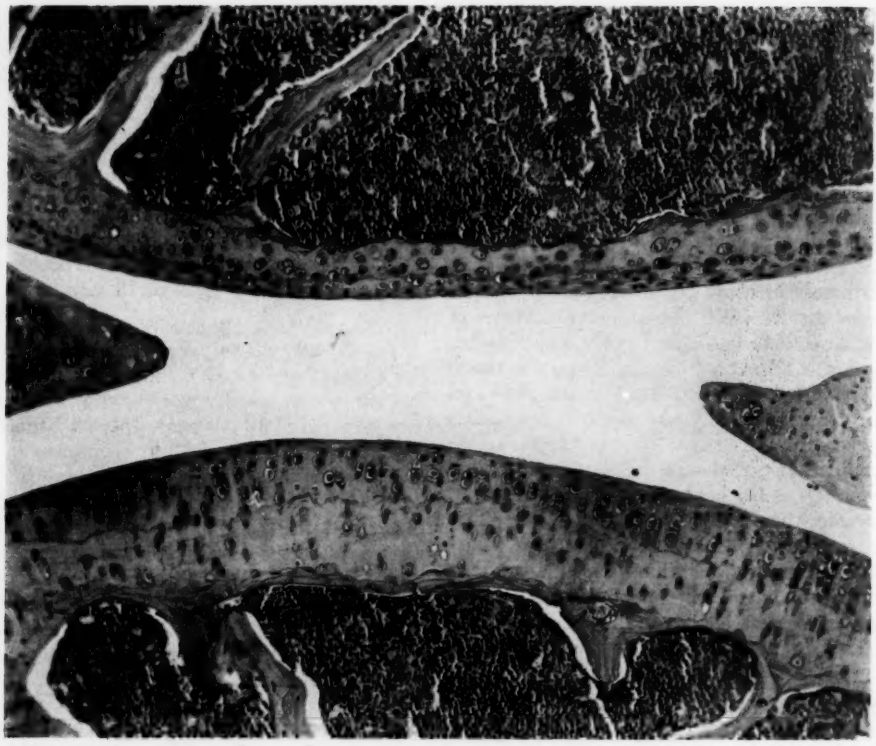

Fig. 1. Unchanged knee joint of a mouse. X112. The articular surfaces are smooth, and the cartilage cells show regular arrangement. Femur on top, tibia on bottom, menisci on either side of photomicrograph.

(c) Microscopic Examination: Osteoarthritis is characterized by either hypertrophic or ulcerative lesions or by a combination of both with involvement of cartilage, ligaments, synovialis, or epiphyseal bone marrow (6).

Figures 1-3 illustrate an unchanged joint and osteoarthritic lesions.

The observations made in animals of the various groups are shown in table 1. The corresponding data obtained previously in stock-fed mice and in mice fed the high-fat ration through life starting at various ages (6) have been included. Since in the present study only mice older than 12 months were examined, animals used in the earlier experiments but younger than 12 months were omitted from this tabulation. In order to permit conclusions as to the age at which joint disease develops, the incidences found at 18 months of age and the total incidences are given separately for each group.

Feeding of the high-fat diet for a period of 5 months from the age of 1 month on accelerated the appearance and somewhat increased the total incidence of osteoarthritis as compared to conditions in untreated controls. At 16.8 months of age about one-third (32.4 per cent) of the stock-fed controls, and at the age of 16.3 months over one-half (52.2 per cent) of the test animals had arthritis. At the end of the second year of life, this difference was less marked. At the age of 19.6 months or 20.6 months, respectively, 44.4 per cent of the stock-fed controls and 59.2 per cent of the animals fed the fat-enriched diet had joint disease.

Feeding of the high-fat diet for 5 months from the age of 6 months on caused a slight increase in the incidence of osteoarthritis from 32.4 per cent to 41.3 per cent at 16.8 or 17.1 months, respectively. Subsequently, the incidence of joint disease was about the same in controls and test animals, namely 44.4 per cent in stock-fed and 47 per cent in the test animals. However, the mean age of the stock-fed mice was 1.4 months higher than that of the mice re-

ceiving the fat-enrichcd ration. Thus, some acceleration of the onset of osteoarthritis was also noticeable in the latter group of animals.

Feeding of the high-fat diet for 5 months from the age of 12 months on did not affect the total incidence of arthritic lesions, 44.4 per cent of the stock-fed and 41.3 per cent of the test animals having joint disease. At 17.9 months of age, 55 per cent of the test mice had osteoarthritis, while of stock-fed controls 16.8 months of age only 32.4 per cent were affected. This increase is actually less striking than it seems because the mice fed the fat-enriched ration were more than 1 month older than the stock-fed controls; yet, a slight acceleration of the disease is recognizable.

Fed for limited periods of time the enriched diet thus essentially accelerated the onset of osteoarthritis without impressively changing the ultimate incidence of the disease. The rapidly developing lesions were as a rule of low grade, while severe and widespread osteoarthritis was rare. Both growing and young adult animals responded more noticeably than mice which had consumed the enriched ration late in life. There was little difference in the effect of the diet if fed from 1 to 6 or from 6 to 11 months, respectively. The 47 per cent incidence of joint disease in young adult mice as compared to the 59.2 per cent incidence seen in growing animals may be due to the 2.4 months difference in age at death. Had the animals of the young adult group lived to a higher mean age, a higher incidence of osteoarthritis might have ensued. In mice of the oldest age group, an acceleration of the joint disease was likewise noted, but the response was, as a whole, not impressive: These animals were at death 0.7 months older than those receiving the diet during the period of growth; yet, the total incidence of osteoarthritis was practically the same as that established for the stock-fed control animals.

Comparison of the Effect of Prolonged and Limited Exposure to the High-Fat Diet

As compared to the effects of prolonged exposure to the fat-enriched ration, feeding of this diet for a period limited to 5 months resulted

Fig. 2. Osteoarthritis in the knee joint of a mouse. X41. Orientation of joint as in fig. 1. The articular surfaces are roughened and irregular in some places. The cartilage is hyperplastic, hypertrophic and degenerated. The insertion of the ligament (central part of the tibia) is distorted.

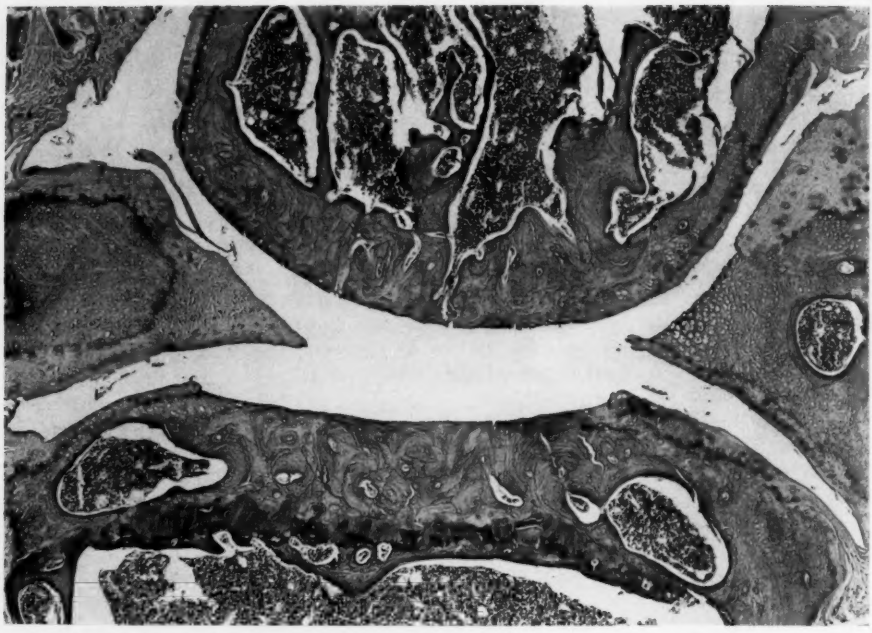

Fig. 3. Ulcerative osteoarthritis advanced in the knee joint of a mouse. X41. Orientation as in previous figures. The surface of the femur is denuded, the underlying bone is bared, eburnated and vascularized; the surface of the tibia likewise shows a deep ulcer with some cartilaginous growth at the margin and eburnation of the bone at the floor of the ulcer.

in delayed onset of the joint disease and in decreased severity of the articular lesions. Thus, while in mice fed the high-fat diet from weaning through life an over-all incidence of 73.1 per cent was noted at a mean age of 18.3 months, only 59.2 per cent were affected at the mean age of 20.6 months, if the diet had been given for a period of 5 months. Similarly, in mice fed the enriched ration from 6 to 11 months, a 47 per cent incidence at 18.2 months compared with an incidence of 71.4 per cent at the mean age of 20.0 months, if the diet was given through life from 6 months of age on. Ultimately, mice fed the high-fat ration from 12 months of age on had at the mean age of 21.3 or 20.7 months, respectively, an arthritis incidence of 41.3 per cent, if the enriched ration was fed for 5 months, and an incidence of 65.6 per cent, if the high-fat diet was continued through life.

DISCUSSION

The harmful effect of the high-fat ration on the articular structures was still noted, if the diet was given for a limited period of time only. Although the damage to the joints was less marked than after prolonged consumption of the fat-enriched ration, the evolution of the articular lesions was accelerated.

The high-fat diet apparently acts in such a way as to cause a prompt response of the susceptible cartilage leading to a rapid appearance of the joint lesions. Low grade lesions apparently may remain stationary for a considerable period of time without progressing to an advanced stage. Whether or not they do increase in severity and also in incidence depends upon such factors as age at the time the dietary regimen is instituted or on the duration of feeding. Young articulations exposed to a high-fat diet suffered greater injury than aged joints, and in animals of all age groups, prolonged exposure proved more injurious than exposure for limited periods of time. Whether or not these observations apply in a general way or only to the conditions of the present experiment will have to be analyzed further.

Old mice gained less weight on the high-fat diet than young mice (7). Probably, therefore, the utilization of ingested fat varied with the age of the animal tested; and the decreased ar-

ticular response may thus partly be related to this age change in metabolism. However, the decreased effectiveness of the fat-enriched ration in old animals may also be due to age changes in the cartilage itself, which loses its reactivity to growth-promoting stimuli with advancing age (2, 5, 6). In mice of strain C57BL, this change becomes apparent sometime during the second half of the first year of life. The onset of this phase may vary from strain to strain and from species to species (1, 2, 4, 5, 6). In growing dogs, regeneration of injured cartilage did not differ from that observed after epiphyseal closure (1, 3). Yet, at the latter stage, the reactivity of the cartilage may be quite different from that of late adulthood or senescence. On the other hand, the growth response of the articular cartilage of acromegalics decreased considerably with advancing age as did that of mice and guinea pigs treated with anterior hypophyseal hormones (2, 6).

SUMMARY

In male mice of strain C57BL, feeding of a diet enriched with 25 per cent lard increased the incidence and accelerated the progress of degenerative joint disease as compared to conditions in stock-fed control animals. Consumption of the high-fat ration for a limited length of time had less injurious effects on the articulations than prolonged consumption of the same diet. The decreased effectiveness manifested itself in a comparatively decreased incidence and severity of the osteoarthritic lesions. The joints of growing mice reacted more noticeably than those of aged mice. The decreased susceptibility of aged joints to the effects of the fat-enriched ration is probably related to a decreased susceptibility to growth-promoting stimuli.

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EFFECT OF SODIUM FLUORIDE ADMINISTRATION ON BODY CHANGES IN OLD RATS

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The purpose of the present study was to determine the effects of feeding of low levels of sodium fluoride from conception until later life on the animal body in old age. Albino rats were used in this research because their normal span of life is less than two years. Furthermore, the albino rat is considered to have a high tolerance against fluoride toxicity. Therefore, one might expect other species to be affected more adversely than this one.

Many communities throughout the nation are introducing fluoride into their water supplies at a level of 1 part per million of fluorine. Such levels are considered safe for lifetime consumption because some natural water supplies which have been used by the population contain more than 5 PPM fluorine.

There is a common assumption that various forms of fluoride are equal in their effect upon the teeth and are similarly absorbed and metabolized. This point of view has been challenged by those who believe that natural waters may contain special forms of fluoride, such as the calcium salt, or that fluorides are modified in their effects by other compounds in the water. Hence, it is questioned whether one can assume equivalence between such compounds as sodium fluoride, silicofluoride, and calcium fluoride.

The belief that there are differences in the effects of fluorides found in various compounds is strengthened by the results of studies with bone meal (4, 19), which indicate that the fluoride in bone meal is rather poorly absorbed. Thus it has been known for some years that bone meal will not protect teeth against erosion from intake of cola beverages, while low levels of sodium fluoride will do so to a limited extent (3, 5, 13). Furthermore, rats and dogs are usually fed for the whole of their lives upon diets rich in bone meal or bone. Nevertheless, in old age one does not see mottled teeth in such animals. Mottled teeth, however, have been produced in both species by feeding of sodium fluoride.

The importance of knowledge about the lifetime ingestion of fluorides and their effect upon the diseases of old age is obvious. Hundreds of investigations deal with short-time ingestion of different levels of fluoride, but as far as we have been able to ascertain the literature contains no reports of studies made on a large number of animals and human subjects throughout the whole life span. Roholm (14) fed high levels of cryolite and sodium fluoride to a small number of rats and dogs for a period of more than 500 days and subsequently studied the injuries produced. An investigation by Auskops and Shaw (1) on fluoride feeding to rats lasted for 11 months, which is somewhat longer than half of the life span for this species; the rats in this study, however, suffered from an epidemic of respiratory diseases. McClure (11) conducted experiments in which rats were given 50 PPM fluorine in their drinking water but were killed at the end of 99 days, which is about 20 per cent of the total life span.

A number of studies have been carried out to determine if loss of teeth from scurvy and from fluoride poisoning may be due to a similar mechanism. Investigators in India (17) have observed that different communities consuming well water with a high fluoride content showed a different incidence of dental injuries. They ascribed this finding to difference in the diet, particularly in the amount of vitamin C consumed by groups with different income levels. They did not, however, consider the possibility of a difference in intake of water or in consumption of tea, which is known to have a high fluoride concentration. Studies by Hauck (6) indicated that ingestion of orange juice might affect the toxicity of fluoride, but the

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levels of fluoride used in their investigations were very high.

Fluoride has been found to accumulate in urinary calculi of man but it has not been determined if fluoride may play a role in initiating the formation of these calculi (7).

MATERIALS AND METHODS

The experiments were designed to evaluate 4 levels of sodium fluoride, 0, 1, 5, and 10 PPM fluorine, administered in the drinking water, which had been distilled. A total of 456 albino rats were included in the investigation. The rats had free access to a given solution at all times. Intake volumes were not measured in the present study.

Two studies were made feeding various groups these different levels of fluorine. Both experiments were started at the beginning of the year, Experiment II being run a year later than the first.

The diet used for all groups had the following composition:

	% of Dry Weight
Toasted wheat flakes	65
Non-fat dry milk solids	10
Soybean oil meal	10
Dried brewers yeast	6
Alfalfa leaf meal	5
Corn oil	2
Mineral mixture*	1
Liver meal	1

One batch of this diet was found to contain 14 PPM flourine from contamination of the various ingredients but the contents of a batch made 3 years later was too low to measure. Fluoride distillations were performed by the method of Singer and Armstrong (15) and determinations of the amount of fluoride carried out by the procedure of Icken and Blank (8).

In Experiment I, 48 pregnant rats were divided into 4 equal groups and the fluoride solutions were administered from the time of conception. The offspring (165 animals) were continued upon the regime after birth until sacrificed. Half of the young in each group were killed at 150 days of age and half at 520 days.

In Experiment II, 72 pregnant rats were used and the same plan followed except that all of the offspring were killed at 150 days of age.

The animals sacrificed at 150 days of age were killed by ether anesthesia, while those in the older group, which were sacrificed at 520 days, were killed by intraperitoneal injection of sodium pentobarbital. This latter procedure was followed in order to perfuse the fixative into the soft tissues of the living animals to prevent post-mortem decomposition. After death the skulls were autoclaved and freed of soft tissue to permit accurate inspection of the teeth. Both femurs were removed for chemical and physical analysis, cleaned, dried, and extracted with ether. Densities were then determined after coating the bones with a thin layer of zein and weighing them in air and in water on an analytic balance in the usual manner. The fluoride analyses on the bones were carried out as described above (8, 15). The thyroids and kidneys of the 520-day-old animals were fixed in Helly's fluid for histologic study.

* The mineral mixture consisted of iodized sodium chloride 454 Gm., calcium carbonate 200 Gm., manganese sulfate 1 Gm., sodium carbonate 1 Gm., ferric oxide 0.5 Gm., and copper sulfate 0.05 Gm.

TABLE 1. EXPERIMENT I—EFFECT OF DIFFERENT LEVELS OF FLUORINE IN THE DRINKING WATER ON THE INCIDENCE OF CARIES IN 86 520-DAY-OLD ALBINO RATS.

Fluorine in the Drinking Water (PPM)	Number of Animals	Number of Animals with Carious Teeth	Number of Carious Teeth	Caries Incidence Ratios*
FEMALES				
0	11	0	0	132/0
1	12	2	2	144/2
5	12	2	6	144/6
10	14	1	1	168/1
MALES				
0	10	0	0	120/0
1	5	1	1	60/1
5	12	4	7	144/7
10	10	3	8	120/8

* The top number indicates total number of molars examined and the bottom number indicates the number of carious teeth observed.

RESULTS AND DISCUSSION

*Teeth**—Experiment I: No evidence of caries was found in the 79 animals which were killed at 150 days of age.

The condition of the teeth of the 86 animals

* The teeth were examined by one of us (C. A. H. Smith).

that were sacrificed at 520 days of age is shown in table 1. It will be seen from the table that no carious teeth were found in the animals that had not received sodium fluoride supplementation. In contrast to this, a substantial number of the rats in each of the groups that had been given sodium fluoride in the drinking water showed carious lesions of the teeth.

There were no missing teeth in the 520-day-old animals that did not receive sodium fluoride in the drinking water, but a considerable number of teeth were missing among those given the additional fluoride (table 2). One rat that had drunk the 5PPM solution of fluorine had lost 5 molars and another rat that had consumed 10 PPM had lost 6. The data in table 2 illustrate the great individual variability in the reactions to sodium fluoride and the need for large numbers of animals to be used in such research.

No evidence of periodontal disease was found among rats sacrificed at 150 days of age.

Only two cases of periodontal disease were observed among the animals killed at 520 days of age which had not received sodium fluoride supplementation in the drinking water. In contrast to this, there was evidence of periodontal disease in all old animals that had been given sodium fluoride in the drinking water, as shown by alveolar bone destruction and increased porosity of the bone. The lesions were as severe in those rats given 5 PPM of fluorine as in the animals receiving the higher level of 10 PPM.

Experiment II: In the second study, which was ended when the animals were 150 days of age, only 3 out of the 281* rats examined showed any caries. One animal with caries was found in each of the groups receiving the lowest level of sodium fluoride in the drinking water, but none in the rats consuming drinking water with the highest fluoride supplementation.

No periodontal disease was observed in any of the animals in this experiment.

These data seem to have no significance except to indicate that 150 days is too short a

* During shipment of the teeth 10 lots were damaged and were consequently excluded from the study.

TABLE 2. EXPERIMENT I: EFFECT OF DIFFERENT LEVELS OF FLUORINE IN THE DRINKING WATER ON THE INCIDENCE OF MISSING TEETH IN 86 520-DAY-OLD ALBINO RATS.

Fluorine in the Drinking Water (PPM)	Number of Animals	Number of Missing Teeth Per Animal
0	21	0
1	14	0
	3	1
5	20	0
	1	1
	1	2
	1	3
	1	5
10	21	0
	2	2
	1	6

TABLE 3. EXPERIMENT I: CORRELATION BETWEEN FLUORINE INTAKE IN THE DRINKING WATER AND WEIGHT AND DENSITY OF FEMURS.

Fluorine in Water (PPM)	Number of Animals	Mean Body Weight (Gm.)	Mean Weight of Dry Femur* (Gm.)	Mean Weight of Dry Fat-Free Femur* (Gm.)	Mean Femur* Density (Gm./ml.)
FEMALES (Killed at 150 days)					
0	11	193.9	.7373	.6960	1.2875
1	13	200.0	.7801	.7336	1.2912
5	9	201.3	.8085	.7711	1.3214
10	13	208.0	.8223	.7848	1.3417
MALES (Killed at 150 days)					
0	9	265.2	.9453	.8949	1.2827
1	7	290.6	.9448	.9028	1.2726
5	11	300.7	1.0165	.9764	1.2767
10	6	290.2	1.0509	.9768	1.2658
FEMALES (Killed at 520 days)					
0	12	236.4	0.9782	0.9077	1.1034
1	12	229.0	0.9425	0.8713	1.0884
5	10	220.2	0.9232	0.8331	1.0596
10	9	233.3	0.9375	0.8867	1.1398
MALES (Killed at 520 days)					
0	10	311.8	1.1988	1.1169	1.0573
1	4	324.5	1.2054	1.1016	1.0302
5	10	360.7	1.2693	1.1373	1.0098
10	10	329.9	1.1961	1.1439†	1.0227

* These figures represent the average from the combined determinations of both the right and left femur.
† Only 4 animals were examined for the dry-fat-free femur weight. The same 4 animals had a mean weight of dry femur of 1.2647.

TABLE 4. EXPERIMENT I: RESULTS OF ADMINISTRATION OF DIFFERENT LEVELS OF FLUORINE IN THE DRINKING WATER ON THE MINERAL AND FLUORIDE CONTENT OF THE FEMURS OF 79 150-DAY-OLD ALBINO RATS.

Fluorine in Water (PPM)	Number of Animals	Mean Wt. of Dry Femur (Gm.)	Mean Wt. of Ashed Femur (Gm.)	Mean Ash Content of Femur (%)	Mean Fluorine Concentration of Ashed Femur (PPM)	Mean Total Fluorine Content of Femur (Micrograms/Femur)
FEMALES						
0	11	.7373	.4396	59.6	152	98
1	13	.7801	.4626	59.3	407	160
5	9	.8085	.4852	61.0	944	425
10	13	.8223	.4923	60.6	1161	572
MALES						
0	9	.9453	.5678	60.1	224	86
1	7	.9448	.5702	60.4	369	201
5	11	1.0165	.6205	61.0	751	461
10	6	1.0509	.6326	60.3	1028	652

period for studies with small animals unless they come from a strain that is very susceptible to tooth decay. Previous studies indicate that our strain prossesses teeth that are relatively resistent even in old age (10).

Density of Femurs.—Data on bone density obtained in Experiment I, in which animals were killed at two different ages, are summarized in table 3. No relation was found between the level of sodium fluoride administered in the drinking water and the density or volume of the femurs in either middle or old age.

The data confirm previous evidence that the bones of the females are denser than those of the males (16). In agreement with earlier observations (2) the younger animals had the denser bones, although the mean weight of the bones was greater for the older animals, which indicates substantial growth in volume of the bones between the ages of 150 and 520 days.

Data on bone density obtained in Experiment II, in which larger numbers of rats were used and in which all were killed at 150 days of age, are not included in table 3 since they did not differ from the observations made in Experiment I.

Fluoride Accumulation in Femurs.—Although it has been known for more than a century that fluoride accumulates in bones, some claims have been made that low levels, such as 1 PPM fluorine in the water, produce little deposition. The question of fluoride storage was also investigated in this study because the basal diet of all animals contained 14 PPM fluorine from the feed ingredients.

TABLE 5. EXPERIMENT I: RESULTS OF ADMINISTRATION OF DIFFERENT LEVELS OF FLUORINE IN THE DRINKING WATER ON THE MINERAL AND FLUORIDE CONTENT OF THE FEMURS OF 77 520-DAY-OLD ALBINO RATS.

Fluorine in Water (PPM)	Number of Animals	Mean Wt. of Dry Femur (Gm.)	Mean Wt. of Ashed Femur (Gm.)	Mean Ash Content of Femur (%)	Mean Fluorine Concentration of Ashed Femur (PPM)	S.D.	Mean Total Fluorine Content of Femur (Micrograms/ Femur)	S.D.
FEMALES								
0	12	0.9782	.5864	59.9	155	±111	90	± 63
1	12	0.9425	.5576	58.9	408	±176	226	±104
5	9	0.9181	.5296	57.5	1399	±526	739	±309
10	11	0.8782	.5483	62.2	3695*	±1241	2057	±881
MALES								
0	10	1.1988	.7120	59.3	202	±134	146	± 94
1	4	1.2054	.7128	58.9	423	±103	304	±106
5	10	1.2693	.7372	58.0	1263	±153	927	±139
10	9	1.2081	.7245	59.8	2312*	±929	1695	±878

* Fluorine values for females were significantly greater than for males at 10 PPM ($P<0.05$).

TABLE 6. EXPERIMENT II: RESULTS OF ADMINISTRATION OF DIFFERENT LEVELS OF FLUORINE IN THE DRINKING WATER ON THE MINERAL AND FLUORIDE CONTENT OF THE FEMURS OF 291 150-DAY-OLD ALBINO RATS.

Fluorine in Water (PPM)	Number of Animals	Mean Wt. of Dry Femur (Gm.)	Mean Wt. of Ashed Femur (Gm.)	Mean Ash Content of Femur (%)	No. of Animals Analyzed for Fluorine	Mean Fluorine Concentration of Ashed Femur (PPM)	Mean Total Fluorine Content of Femur (Micrograms/ Femur)
FEMALES							
0	30	.8633	.5193	60.1	16	53	27
1	46	.8542	.5196	60.8	13	136	68
5	43	.8217	.4939	60.1	17	632	302
10	30	.8273	.4981	60.2	17	1092	557
MALES							
0	27	1.1268	.6809	60.4	14	65	44
1	52	1.0925	.6603	60.4	18	165	108
5	37	1.0841	.6475	59.7	12	626	398
10	26	1.0929	.6642	60 8	11	770	493

The data listed in tables 4, 5, and 6 indicate that the storage of fluoride was proportional to the level of fluoride in the drinking water and to the length of time the fluoride was administered. This time effect was especially marked for the two higher levels of fluorine.

Comparison of the results presented in tables 4 and 6 illustrates the degree of reproducibility of observations in repeated experiments. In Experiment II the effect of the lowest level of sodium fluoride intake on fluoride storage is less evident, although the storage was of the same order of magnitude as in Experiment I.

The differences between the sexes in the storage of fluoride are marked, especially in the groups given the two higher levels of fluorine, the female storing more than the male. Such sex differences have also been noted in the research of others (12). One possible explanation for this difference is that the female rats ingest more fluid than the males (10).

*Thyroids and Kidneys.**—Only a limited number of the thyroids were examined since no evidence of changes was found either macroscopically or microscopically.

No gross lesions were found in the kidneys. Microscopic examinations were made on the kidneys from 6 animals which had not received fluoride in the drinking water, on 3 receiving 1 PPM, on 1 receiving 5 PPM, and on 6 receiving 10 PPM.

* The authors are attempting to arrange for an extensive study of the kidneys of animals from these experiments.

Interstitial nephritis was observed in all the animals examined histologically, and the severity increased in proportion to the level of the sodium fluoride in the drinking water. Renal tubule hypertrophy and hyperplasia were found in those animals receiving sodium fluoride in the water but not in the 6 rats which had not been given sodium fluoride supplementation. The hypertrophic and hyperplastic changes consisted of large numbers of newly formed hyperchromatic tubule cells, which in places were more than one layer deep. The nuclei were much larger than those of normal cells; there were a few mitotic figures (fig. 1, and 2). This histologic picture is usually considered to represent tissue regeneration following a loss of degenerate or necrotic cells. However, inasmuch as no necrosis was observed in these kidneys, a possible stimulation of the tubule cells to proliferate, directly or indirectly by the fluoride, must be considered.

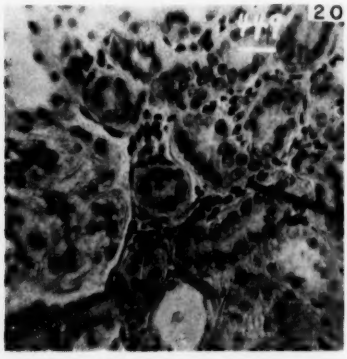

Fig. 1. Photomicrograph of a section of a kidney from albino rat No. 449 that had received 10 PPM. fluorine as sodium fluoride in the drinking water for a period of 520 days. Renal tubule cell hypertrophy and hyperplasia can be observed near the pointer. These cells seem to indicate a loss of polarity with nuclei that are larger than normal. 330 X.

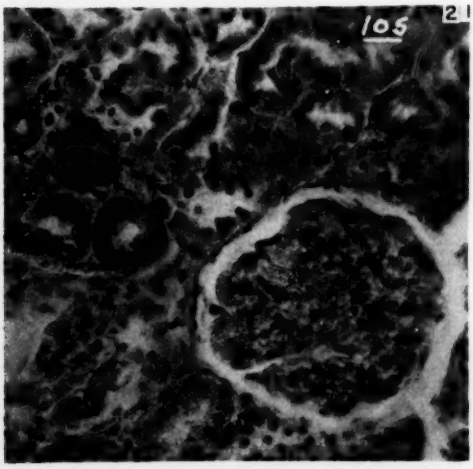

Fig. 2. Photomicrograph of a normal kidney taken from albino rat No. 105 that had no flourine added to the water supply for the 520 days of its life span. 440 X.

SUMMARY

The effects of feeding low levels of sodium fluoride from conception until old age were determined in a total of 456 albino rats. Four levels of sodium fluoride (0, 1, 5, and 10 PPM fluorine) were given to 4 groups of animals in their drinking water. In one study half of the rats were killed at 150 days of age and half at 520 days. In the second experiment all rats were killed at 150 days.

No evidence of injury to the teeth was found in the animals killed at 150 days of age, but marked injury was noted in those given sodium fluoride supplementation until they were 520 days old. In old age missing teeth and periodontal disease were frequent in rats which had received sodium fluoride supplementation, especially at the higher levels. Sodium fluoride supplementation at low levels did not affect the density nor the volume of the femurs. Fluoride accumulated in the femurs in direct proportion to the level in the drinking water and the length of time the animals lived, the females storing more fluoride than the males. No macroscopic or microscopic changes were observed in the thyroid gland. Hypertrophy and hyperplasia of the kidney tubules were found in rats receiving fluoride but were not observed in the unsupplemented animals.

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MUCOPOLYSACCHARIDES OF HUMAN ARTERIAL TISSUE

I. Isolation of Mucopolysaccharide Material*

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The preparation of chondroitin sulfuric acid from the aorta of cattle was described in 1918 by Levene and López-Suarez (5, 6). Jorpes and his coworkers (2, 3,) in 1937 isolated heparin from aortic tissue of the pig and ox. A study of arterial mucopolysaccharides was later carried out by Meyer and Rapport (11), who reported the isolation of chondroitin sulfate B and C from animal aortic tissue. According to recent investigations by Meyer (7, 8) chondroitin sulfate A, hyaluronic acid, and a mucopolysaccharide fraction containing N-acetylglucosamine, uronic acid, and sulfate have also been demonstrated in the bovine aorta.

No investigations have as yet been reported on mucopolysaccharides isolated from human arterial tissue. The present and subsequent articles deal with studies carried out on human arterial mucopolysaccharides.

METHOD

For isolation of the mucopolysaccharides from human aortic tissue a modification of the techniques described by Meyer and his associates (9, 10) and by Pearce and Watson (13) was used. Thirty aortic samples were obtained fresh at autopsy at the St. Louis City Morgue.† The age of the individuals from whom the samples were derived ranged from 1 to 76 years. In the case of samples obtained from adults both the ascending and descending thoracic portions were used, yielding an amount of 10 to 30 Gm. of tissue. Because of the smaller quantity of tissue obtainable from children, the abdominal aorta was employed in addition to the thoracic aorta, giving an amount of tissue of about 2 to 4 Gm. After removal of the adventitia the intima-media part of the blood vessels were stored in air-tight glass containers which were maintained at −20 C. until used.

Reagents

1) Hydrochloric acid, 4 N; 2) Pepsin, powder, N.F. (Fisher Sc. Co.); 3) Toluene; 4) Sodium hydroxide, 4 N; 5) Trypsin, purified (Fisher Sc. Co.); 6) Hyflo-Super Cel (Johns Manville Co.); 7) Precipitation mixture: 1 Gm. of potassium acetate is dissolved in 100 ml. of 95 per cent ethyl alcohol, and 1.0 ml. of glacial acetic acid is added; 8) Calcium chloride solution, 10 per cent; 9) Chloroform-amyl alcohol reagent: To 4 volumes of chloroform is added 1 volume of N-amyl alcohol; 10) Acetic acid, 1 N; 11) Lloyd's reagent (Harleco); 12) Sodium acetate solution, 1 per cent; 13) Alpha-amylase (Nutritional Biochemicals Corp.); 14) Calcium acetate buffer solution: 5 Gm. of calcium acetate are dissolved in 100 ml. of 0.5 N acetic acid; 15) Ethyl alcohol, 95 per cent; 16) Barium chloride ($BaCl_2$, 2 H_2O) solution, 1 per cent; 17) Sodium carbonate solution, 1 per cent; 18) Sodium rhodizonate solution, freshly prepared, containing approximately 0.5 mg. of sodium rhodizonate per milliliter.

*Procedure**

After thawing of the sample the tissue was weighed and transferred to a Waring blendor. To the sample in the blendor were added 5 volumes of distilled water, after which the tissue was homogenized for 20 minutes. For homogenization of the aortic samples from children ordinary Pyrex glass grinders were used.

The homogenate was transferred to an Erlenmeyer flask, and the blendor or homogenizer rinsed with several sets of distilled water, which were added to the homogenate. Sufficient water was used so as to make a final tissue concentration of approximately 10 per cent.

The pH of the homogenate was adjusted to 1.5 by addition of 4 N hydrochloric acid, using external shielded glass electrodes. Twenty mg. of powdered pepsin were then added per gram of wet tissue, and, after mixing, the sample was covered with a layer of toluene and placed in a thermostat at 37 C. for 72 hours.

At the end of the 72-hour digestion period the sample was neutralized by addition of 4 N sodium hydroxide (final pH 7.0 to 8.0), and 30 mg. of trypsin were added per gram of wet tissue. The sample was then returned to the thermostat for a period of 24 hours.

After completion of the enzymatic treatment approximately 0.5 Gm. of Hyflo-Super Cel was added per gram of tissue. The sample was shaken and was afterwards filtered by the use of suction through two layers of Whatman No. 42 filter paper placed in a Buchner funnel. The resulting, practically clear *filtrate* was then transferred to a beaker and evaporated at 75 to 85 C. on an asbestos covered electric hot plate till of syrupy consistency. The volume was recorded and the sample transferred with a minimum amount of water to a 250 ml. centrifuge tube (Arthur H. Thomas Co., Catalogue No. 3139-A).

For precipitation of the mucopolysaccharides from the solution 2 volumes of precipitation mixture were added. The centrifuge tube was stoppered, and the contents were mixed gently for 2 to 3 minutes, after which the sample was placed in the refrigerator at −20 C. for 12 hours to complete the precipitation.

The sample was subsequently centrifuged for 15 minutes at 5000 r.p.m., and the supernatant discarded; the centrifuge tube was inverted and placed for 5 minutes on filter paper to complete the drainage of the supernatant. The *precipitate* was then suspended by brief shaking in 50 ml. of 10 per cent calcium chloride, and 10 ml. of chloroform-amyl alcohol mixture were added, after which the centrifuge tube was stoppered. During the following 48 hours the sample was maintained at room temperature and was shaken intermittenly; it was then centrifuged for 15 minutes at 5000 r.p.m. The precipitate was discarded and the *supernatant* decanted into 100 ml. of precipitation mixture contained in a 250 ml. centrifuge tube. After shaking, the sample was placed in the refrigerator at −20 C. for 12 hours.

The sample was again centrifuged (15 min., 5000 r.p.m.), and the supernatant discarded. The *precipitate* was dissolved in 20 ml. of 1 N acetic acid solution. One Gm. of Lloyd's reagent was then added, and the centrifuge tube was shaken vigorously for 5 to 10 minutes. Following this the sample was centrifuged (15 min., 5000 r.p.m.) and

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† The authors are indebted to Dr. J. J. Connor for assistance in obtaining specimens.

* For the sake of clarity the fractions which contain the mucopolysaccharides have been italicized.

the *supernatant* poured into a second centrifuge tube, containing 60 ml. of precipitation mixture. The precipitate in the first centrifuge tube was again shaken with 10 ml. of 1 N acetic acid solution for further extraction of mucopolysaccharides, and the centrifugation was repeated. The *supernatant* resulting from this centrifugation was then added to the 60 ml. of precipitation mixture in the second centrifuge tube. This latter tube, containing the mucopolysaccharides from the two extractions, was placed in the refrigerator at —20 C. for 12 hours.

At the end of the 12 hours' refrigeration the sample was centrifuged for 15 minutes at 5000 r.p.m., and the supernatant was discarded. The *precipitate* was dissolved in 10 ml. of a 1 per cent solution of sodium acetate, and a few mg. of alpha-amylase and 5 drops of toluene were added. The sample was then incubated in the thermostat at 37 C. for 5 to 6 hours, after which 20 ml. of precipitation mixture were added. Following shaking of the sample the centrifuge tube was placed in the refrigerator at —20 C. for 12 hours.

The sample was again centrifuged (15 min., 5000 r.p.m.) and the supernatant discarded. The *precipitate* was dissolved by shaking in 10 ml. of calcium acetate-buffer solution. From this solution the mucopolysaccharides were precipitated by addition of 35 ml. of 95 per cent ethyl alcohol, and the sample was placed in the refrigerator at —20 C. for 12 hours. After centrifugation (15 min., 5000 r.p.m.) the *precipitate* was dissolved in 10 ml. of redistilled water. The solution was again centrifuged (15 min., 5000 r.p.m.) and the clear *supernatant* carefully decanted.

For removal of inorganic sulfate and phosphate from the mucopolysaccharide solution the following technique was employed, which is based in part on the procedure described by Vansteenberghe and Bauzil (14). The glassware used for this purification had been cleaned in boiling hydrochloric acid followed by rinsing with several sets of redistilled water.

To 2 volumes of the mucopolysaccharide solution contained in a centrifuge tube was added 1 volume of 1 per cent barium chloride solution. After 30 minutes the sample was centrifuged for 5 minutes. The removal of inorganic sulfate from the solution was ascertained by adding a drop of barium chloride solution to the supernatant. The *supernatant* was carefully decanted into another centrifuge tube, and 1 volume of 1 per cent sodium carbonate solution was added. After gentle mixing of the contents the tube was placed in a water bath at 60 C. for 15 minutes. The precipitate resulting from the carbonate addition was removed by centrifugation (5 min.) and subsequent filtration of the *supernatant* through a Whatman No. 40 ashless filter paper. The absence of barium from the *filtrate* was checked by means of the sodium rhodizonate reaction, which was carried out at 60 to 70 C. in a 80 to 90 per cent ethyl alcohol medium as outlined by Øllgaard (12).

For determination of the mucopolysaccharide content of the isolated material the turbidimetric procedure of Di Ferrante (1) was employed, using as reference standard a commercial chondroitin sulfate preparation (Aldrich Chemical Co., Inc.) from tracheal cartilage of cattle. The uronic acid content of this preparation, determined gasometrically, was used for calculation of the true mucopolysaccharide content of the standard. The average difference between duplicate analyses was 2.9 per cent. It was ascertained by means of the Di Ferrante technique that no significant loss of mucopolysaccharide material occurred as the result of the barium chloride-sodium carbonate treatment of the samples.

RESULTS

The quantities of mucopolysaccharide material obtained by the isolation procedure from aortic samples of various age groups are listed in table 1. An average amount of 4.9 mg. mucopolysaccharide /Gm. wet tissue was isolated from the aortas of children, and 4.8 mg./Gm. wet tissue from the samples derived from individuals aged 20 to 59 years. The yield from the aortas of 60 to 76 year old subjects was distinctly lower (2.4 mg./Gm. wet tissue).

TABLE 1. MEAN YIELD OF MUCOPOLYSACCHARIDE MATERIAL FROM AORTIC SAMPLES OBTAINED FROM INDIVIDUALS OF VARIOUS AGE GROUPS.

Age Group (Years)	Number of Samples	Quantity of Tissue Used (Gm.)	Quantity of Mucopolysaccharide Obtained		Percentage Yield	
			Mg.	Mg./Gm. Wet Tissue	I*	II†
0- 9	5	2.5	12.2	4.9	34.7	56.0
20-39	5	11.7	61.2	5.2	34.9	71.5
40-49	5	13.2	51.9	3.9	39.3	60.8
50-59	9	16.7	66.0	4.0	33.9	66.7
60-76	6	22.9	54.2	2.4	24.6	47.4

* Calculated on the basis of hexosamine analyses.
† Calculated on the basis of acid-hydrolyzable sulfate analyses.

Calculations were further made of the percentage yield of mucopolysaccharides, estimated by comparison of the hexosamine and acid-hydrolyzable sulfate concentrations of the fresh tissue and of the isolated material. The results of these calculations have likewise been entered in table 1. It was found that the mean mucopolysaccharide yield for the 30 aortic samples was 33.1 per cent, when estimated on the basis of the hexosamine analyses, and 60.9 per cent, when calculated on the basis of the sulfate determinations. The fact that in a previous study (4) a considerable portion of the hexosamine in human aortic tissue could not be accounted for on the basis of the acid-hydrolyzable sulfate content of the tissue may be of significance in connection with the observed difference in the calculated percentage yields.

SUMMARY

A procedure is described for isolation of mucopolysaccharide material from human arterial tissue. The technique is a modification of the methods developed by Meyer and his associates and by Pearce and Watson.

The average yield of mucopolysaccharide material was 4.9 mg./Gm. wet tissue from the aortas of children, 4.8 mg./Gm. wet tissue from aortic samples of individuals aged 20 to 59 years, and 2.4 mg./Gm. wet tissue from aortas of 60 to 76 year old subjects.

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MUCOPOLYSACCHARIDES OF HUMAN ARTERIAL TISSUE

II. Analysis of Total Isolated Mucopolysaccharide Material*

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In the accompanying paper (5) the isolation of mucopolysaccharides from 30 samples of human aortas was reported. The present study was undertaken with the purpose of characterizing the mucopolysaccharide material through determination of the total hexosamine, galactosamine, glucosamine, uronic acid, sulfate, and protein content of the samples. In addition, the effect of testicular and bacterial hyaluronidase on the arterial mucopolysaccharides was investigated.

METHODS

Total Hexosamine, Galactosamine, and Glucosamine

For measurement of the total hexosamine, galactosamine, and glucosamine concentrations of the aortic mucopolysaccharide samples solutions in distilled water were prepared containing 5-10 mg. of mucopolysaccharide per milliliter. One hundred cu. mm. of the solution were measured into a 10 ml. glass ampoule by means of a constriction pipette, and 0.9 ml. of distilled water and 1.0 ml. of 4 N hydrochloric acid were added. The ampoule was sealed and placed in a constant temperature oven at 118 C. for 2 hours. After cooling, the hydrolysate was diluted to 10.0 ml. with water. One portion of the hydrolysate was used for colorimetric determination of total hexosamine, as previously described (9). For estimation of the galactosamine and glucosamine contents of the sample a 5.0 ml. portion of the diluted hydrolysate was evaporated to dryness in a 10 ml. beaker placed in a vacuum desiccator supplied with sodium hydroxide pellets for absorption of the hydrochloric acid vapors and with anhydrous magnesium perchlorate for absorption of the water. The dry residue was subsequently dissolved in 200 cu. mm. of distilled water. The resulting solution was employed for separation of galactosamine and glucosamine hydrochlorides by paper chromatography.

The chromatographic procedure used was in most respects similar to that described by King and Hyder (8). This method employs ascending chromatography and the use of 2,6-lutidine (90 per cent, practical, Eastman Kodak Co.): water (65 : 35) as solvent. In the present investigation the chromatograph chamber used consisted of a rectangular Pyrex glass jar of 10x12 x24 inch dimensions (Research Equipment Corp., Oakland, Calif.).

Successive 5 cu.mm. portions of the test solution were applied to Whatman No. 1 paper strips of 50 cm. length by means of a constriction pipette, the spot on the paper being dried with a current of air after each application. As reference standards 50 microgram samples of galactosamine hydrochloride* and glucosamine hydrochloride (5 cu.mm. of a 1 per cent solution) were employed. Under the conditions used by the authors the best separation of galactosamine and glucosamine was obtained after 40 hours' chromatography at room temperature (fig. 1). At the end of the experiment the paper strips were dried at room temperature for 12 hours. For development of the chromatograms the strips were sprayed with a freshly prepared 0.2 per cent solution of ninhydrine in dry acetone, using a De Vilbiss Burn Atomizer with Bulb #261. The sprayed paper strips were left for 5 to 10 minutes for evaporation of the acetone and were afterwards stored in the dark for 12 hours for maximum color development. The color intensity of the spots was measured by means of a Spinco Analytrol recording photometer and automatic integrator, using Corning glass filters No. 3486. The apparatus was standardized for these measurements by densimetric determinations performed on galactosamine and glucosamine hydrochloride standards of various concentrations, which had been carried through the complete chromatographic procedure.

With the use of the chromatographic technique described above R_f values for the galactosamine hydrochloride and glucosamine hydrochloride standards of, respectively, 0.44 (range, 0.43 to 0.47) and 0.50 (range, 0.49 to 0.52) were found. The R_f value observed for glucosamine hydrochloride in the present experiment (0.50) is of the same order of magnitude as that reported by King and Hyder (0.41 to 0.45), whereas the R_f value of 0.44 found for galactosamine hydrochloride differs significantly from the value of 0.21 to 0.23 given by these authors.

In the application of the chromatographic technique to the acid hydrolysates of the aortic mucopolysaccharide samples two distinct spots were regularly observed (fig. 2). The average R_f value observed for the faster moving fraction was 0.50, and for the slower moving fraction 0.44. It should be noted that very small quantities of extraneous amino acids were found on chromatography of the arterial mucopolysaccharide samples, a fact which indicates the purity of the isolated material.

Uronic Acid

For determination of the uronic acid content of the isolated mucopolysaccharide material two procedures were used, the colorimetric method of Dische (3, 4), employing reaction with carbazole in 87 per cent sulfuric acid, and a modification of Tracey's (14) gasometric method.

For the colorimetric analyses tubes provided with ground glass stoppers were used. This permitted thorough shaking of the samples after addition of the carbazole reagent, a step of the procedure which was

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* The authors are indebted to Dr. S. Roseman, University of Michigan, for a supply of pure galactosamine hydrochloride.

found essential for satisfactory color development. A chondroitin sulfate preparation (Aldrich Chemical Co., Inc.) (5) was used as reference standard. The average difference between duplicate analyses was 2.7 per cent.

For gasometric uronic acid determination a modification of Tracey's method was developed in which commercial, long-necked glass ampoules of 10 ml. capacity instead of specially prepared glass tubes were used. The ampoules were cleaned before use with hot chromic-sulfuric-phosphoric acid solution (15). Following the cleaning with acid the ampoules were rinsed with several sets of tap water and distilled water and dried.

A 2 to 5 mg. sample of the mucopolysaccharide material, dissolved in 2.0 ml. of distilled water, was placed in the ampoule, and 1.0 ml. of concentrated hydrochloric acid was added. The carbon dioxide present in the solution was removed by connecting the neck of the ampoule by means of a piece of vacuum tubing with a vacuum pump and exposing the sample to high vacuum for 1 minute. After the evacuation air was allowed to reenter the ampoule. The ampoule was subsequently sealed under conditions preventing carbon dioxide from the gas flame from entering the ampoule.

The liberation of carbon dioxide from uronic acids was effected by placing the sealed ampoule for 5 hours in a constant temperature oven maintained at 118 C.

For determination of the liberated quantity of carbon dioxide a procedure was used similar to that described by Van Slyke, Page and Kirk (15). The closed ampoule was attached to the capillary outlet of the stop-cock of the Van Slyke chamber by means of a special connection piece. This consisted of 5 cm. of soft rubber tubing and 8 cm. of vacuum tubing joined by a short length of glass tubing. The soft rubber tubing was fastened to the neck of the ampoule, whereas the vacuum tubing served for attachment to the capillary outlet of the chamber stop-cock. When air-tight connection had been established the neck of the ampoule was broken near its tip by applying a Kelly forceps to the soft rubber tubing. The main portion of carbon dioxide in the ampoule was transferred to the sodium hydroxide solution in the extraction chamber by lowering and raising the mercury in the chamber 5 times. The gas pressure in the system was then brought to about 400 mm. Hg, after which the ampoule was heated for 20 seconds with an alcohol burner, the connection between the ampoule and the extraction chamber remaining open. Following the heating of the sample the mercury in the chamber was again lowered and raised 5 times. The greater part of the unabsorbed gas was then ejected without loss of fluid, and vacuum was produced in the chamber by lowering the mercury. The final traces of carbon dioxide were subsequently transferred from the ampoule to the alkali in the chamber by lowering and raising the mercury 5 times, the gas pressure during this stage being approximately 30 mm. Hg. The ampoule was then disconnected from the chamber and the unabsorbed gas ejected. The determination of the carbon dioxide content of the alkali solution was carried out in the usual way (15).

A sample consisting of 2.0 ml. of distilled water and 1.0 ml. of concentrated hydrochloric acid contained in an ampoule treated in the same way as the test samples served as a blank.

The average difference between duplicate analyses was 2.4 per cent.

Since prolonged heating with acid may cause further decomposition of the uronic acid investigations were conducted to establish the optimal period of heating under the conditions employed in the procedure. For this purpose 5.0 mg. samples of sodium glucuronate (equivalent to 4.45 mg. of glucuronic acid) were heated with hydrochloric acid for periods ranging from one-half to 6 hours. The results of the analyses, presented in table 1, show a 96 per cent yield of carbon dioxide after 3 hours of heating, and a 100 per cent yield after 5 hours.

TABLE 1. THE EFFECT OF TIME OF HYDROLYSIS ON THE QUANTITY OF CARBON DIOXIDE LIBERATED FROM SODIUM GLUCURONATE.

Time of Hydrolysis (Hours)	Mg. CO_2 Found in Sample	Mg. Glucuronic Acid Found in Sample	Per Cent of Theoretical
0.5	0.313	1.37	31
1.0	0.594	2.60	58
2.0	0.930	4.07	92
3.0	0.970	4.25	96
4.0	0.999	4.36	98
5.0	1.015	4.45	100
6.0	0.990	4.32	97

Sulfate

For determination of the sulfate (SO_4) content of the mucopolysaccharide samples 0.5 to 1.5 mg. of the material was hydrolyzed with hydrochloric acid as described in a previous publication (9). Following hydrolysis the samples were evaporated to dryness in a vacuum desiccator, which contained sodium hydroxide pellets for absorption of the hydrochloric acid vapors and anhydrous magnesium perchlorate for absorption of the water. The residue was dissolved in 6.0 ml. of distilled water and the pH of the solution adjusted to 4-5. The solution was subsequently filtered through a Whatman No. 40 ashless filter paper.

The sulfate determinations were carried out on the hydrolyzed samples by a modification of Hoagland's (6) procedure. A 2.0 ml. aliquot of the solution was measured into a Hoagland tube, and 1.0 ml. of 1.6 per cent benzidine hydrochloride solution in 0.2 N hydrochloric acid was added, followed by 6.0 ml. of dry acetone. The tube was placed in the refrigerator for 12 hours for precipitation of benzidine sulfate and was then centrifuged for 15 minutes at 5000 r.p.m. After centrifugation the supernatant was carefully poured off and the tube inverted on clean filter paper for 10 minutes. Four ml. of 90 per cent acetone were then added slowly with a pipette, the acetone being allowed to drain down the inside of the tube. After the acetone addition the tube was centrifuged for 5 minutes. The rinsing with acetone and centrifugation were repeated, after which the supernatant was poured off and the inverted tube allowed to drain off remaining traces of fluid on a filter paper. Ten ml. of 0.2 N hydrochloric acid were then added, and the tube was closed tightly with a ground glass stopper. The benzidine sulfate precipitate was brought into solution by heating the tube for 30 to 90 minutes in a boiling water bath.

After cooling, the benzidine content of the sample was determined by measuring the absorption of the solution at 248 millimicrons, using a Beckman DU

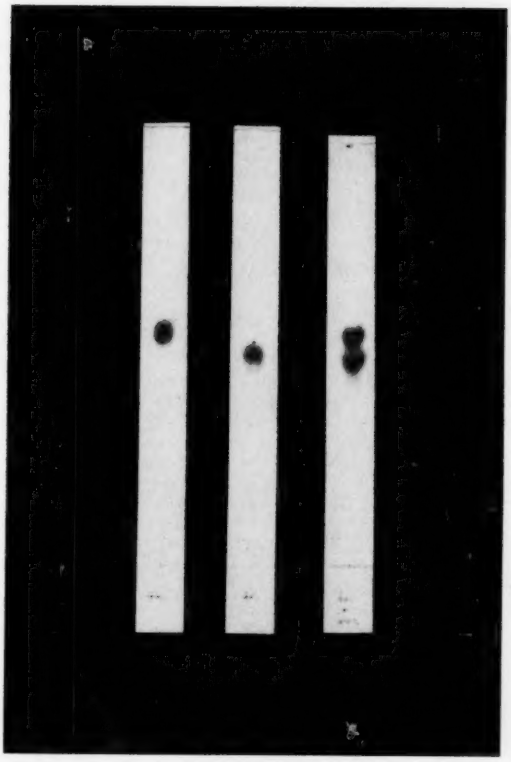

Fig. 1. Paper chromatograms of glucosamine, galactosamine, and glucosamine + galactosamine hydrochloride standard solutions. Applied dose, 50 micrograms.

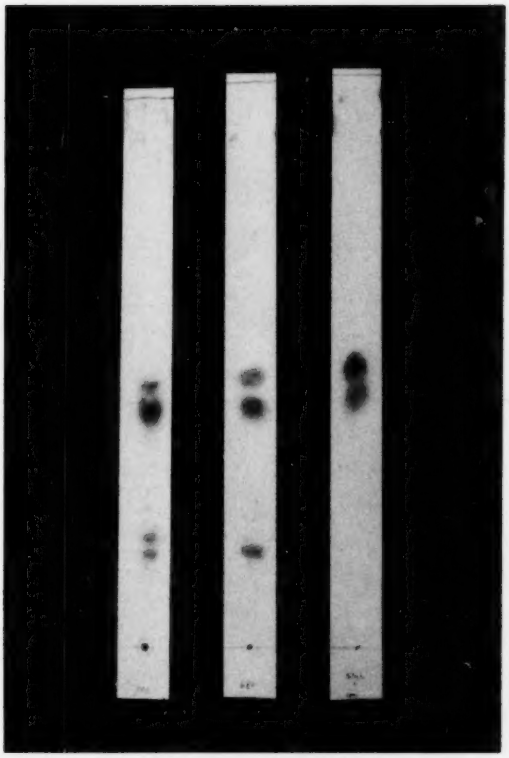

Fig. 2. Paper chromatograms of hydrolysates of mucopolysaccharides isolated from human aortic tissue (Samples No. 30 and 26) and of glucosamine + galactosamine hydrochloride standard solution.

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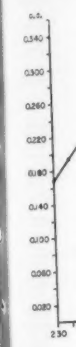

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spectrophotometer. The molar extinction coefficient of benzidine in 0.2 N hydrochloric acid solution at this wave length is 18,700. The absorption spectrum of a 0.5 mg. per cent solution of benzidine sulfate in 0.2 N hydrochloric acid is shown in figure 3.

A 2.0 ml. sample of distilled water, carried through the whole procedure, served as a blank.

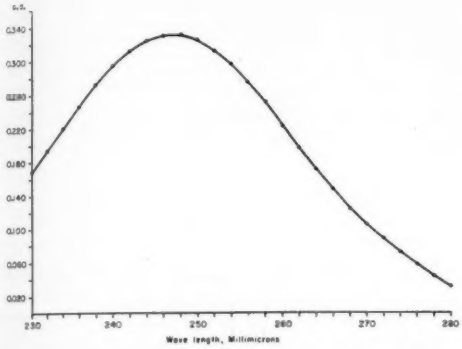

Fig. 3. Absorption spectrum of 0.500 mg. per cent solution of benzidine sulfate (corresponding to 0.326 mg. per cent solution of benzidine) in 0.2 N hydrochloric acid. Light path, 10 mm. Readings made against cuvette containing 0.2 N hydrochloric acid solution.

Protein

The protein content of the mucopolysaccharide samples was determined by the method of Lowry, Rosenbrough, Farr, and Randall (10).

Determination of Hydrolysis of Mucopolysaccharides by Testicular and Bacterial Hyaluronidase

Experiments were conducted on 4 samples of arterial mucopolysaccharides with testicular (Alidase, Searle) and bacterial (staphylococcal) hyaluronidase (Hyason, Organon*), using a reductometric procedure. The activity of the hyaluronidase preparations was ascertained by the viscosimetric method of Dalgaard-Mikkelsen and Kvorning (2), using commercial chondroitin sulfate and hyaluronic acid preparations as substrates.

In the studies with arterial mucopolysaccharides 5 to 8 mg. of material dissolved in 3.5 ml. of distilled water were employed for each test. In the experiments with testicular hyaluronidase a quantity of enzyme having an activity of 350 viscosity units was dissolved in 3.5 ml. of 0.1 N acetate buffer of pH 6.0. For the investigations with bacterial hyaluronidase 210 turbidity units in 3.5 ml. of acetate buffer were used.

Before the experiment was begun the mucopolysaccharide and hyaluronidase solutions were preheated in a water bath at 38 C. for 10 minutes. The experiment was started by mixing of the solutions, after which the tubes were returned to the water bath. Aliquots were removed at 0, 1, 3, and 8 hours for determination of reducing substances. Immediately after removal of the samples the hyaluronidase was inactivated by heating of the solution for 3 minutes in a boiling water bath.

The quantity of reducing substances was determined by the procedure of Nelson (12), employing the reagents described by Somogyi (13). The measurements were carried out spectrophotometrically at 750 millimicrons, using cuvettes with a 25 mm. light path.

The reduction values of the hyaluronidase solutions were subtracted from the values obtained in the experiments. Control tests were performed in which solutions of mucopolysaccharide and hyaluronidase were maintained separately at 38 C. No increase in the reduction values of these solutions was observed over an 8 hour period.

TABLE 2. COMPOSITION OF ISOLATED MUCOPOLYSACCHARIDE MATERIAL FROM INDIVIDUAL AORTIC SAMPLES.

Sample No.	Age (Yrs)	Total Hexosamine %	Galactosamine		Glucosamine		Uronic Acid %		SO_4 %	Protein %
			% of Hexosamine	R_f	% of Hexosamine	R_f	Colorimetric	Gasometric		
1	1	27.8	75	0.44	25	0.50	32.9	29.1	10.4	1.4
2	3	33.8	82	0.46	18	0.52	40.7	....	8.9	1.9
3	3	20.5	78	0.44	22	0.50	33.1	....	13.4	0.0
4	5	26.6	79	0.47	21	0.53	28.9	29.3	12.3	2.8
5	8	24.1	72	0.47	28	0.53	33.5	35.1	14.7	1.0
	Mean	26.6	77	0.46	23	0.52	33.8	31.2	11.9	1.4
6	25	21.5	69	0.43	31	0.49	27.8	21.7	11.8	1.1
7	29	28.8	78	0.44	22	0.49	39.9	39.9	8.7	1.8
8	33	25.3	77	0.42	23	0.48	35.6	33.8	15.4	1.1
9	38	21.7	74	0.43	26	0.49	31.3	33.6	11.0	1.0
10	39	20.7	61	0.43	39	0.48	32.7	36.9	11.2	1.2
	Mean	23.6	72	0.43	28	0.49	33.5	33.2	11.6	1.2
11	41	31.7	69	0.45	31	0.51	34.4	38.9	12.0	0.9
12	46	22.6	81	0.44	19	0.49	26.3	30.3	9.3	2.5
13	46	23.4	88	0.41	12	0.47	33.1	34.7	10.3	1.0
14	49	30.5	78	0.40	22	0.46	41.5	39.9	12.3	2.8
15	49	25.8	76	0.40	24	0.46	34.4	33.3	10.0	2.2
	Mean	26.8	78	0.42	22	0.48	33.9	35.4	10.8	1.9
16	50	26.1	83	0.46	17	0.53	31.5	32.9	8.8	2.4
17	50	21.5	87	0.47	13	0.53	31.5	35.7	13.0	0.9
18	51	22.4	75	0.47	25	0.53	29.8	33.7	12.2	1.4
19	52	22.0	77	0.41	23	0.46	33.0	32.8	10.9	1.8
20	53	25.6	85	0.40	15	0.45	39.4	35.9	12.0	1.2
21	53	23.3	86	0.45	14	0.51	32.5	32.8	15.1	1.7
22	54	24.7	81	0.41	19	0.47	32.7	32.9	10.1	2.9
23	56	27.7	85	0.46	15	0.52	30.7	34.4	14.8	2.7
24	58	23.3	61	0.45	39	0.51	33.7	33.2	15.6	1.8
	Mean	24.1	80	0.44	20	0.50	32.8	33.8	12.5	1.9
25	65	22.9	90	0.44	10	0.49	29.9	31.4	13.2	1.2
26	66	22.3	82	0.41	18	0.46	31.5	31.1	11.6	2.0
27	68	25.7	86	0.43	14	0.48	37.6	34.3	12.1	0.9
28	76	22.4	91	0.46	9	0.52	30.9	31.4	14.1	2.0
29	76	22.5	79	0.44	21	0.50	31.1	30.2	14.3	1.8
30	76	26.6	85	0.42	15	0.47	36.1	36.8	15.7	2.0
	Mean	23.8	85	0.43	15	0.49	32.9	32.5	13.5	1.7

* The authors are indebted to Dr. K. W. Thompson, Organon, Inc., Orange, N. J., for the supply of samples of bacterial hyaluronidase.

RESULTS

The results of analyses performed on the individual arterial mucopolysaccharide samples have been listed in table 2; table 3 contains the mean values observed for the various age groups. It will be seen from the reported values that the average total hexosamine concentration found was 24.8 per cent. It is of significance to note that galactosamine averaged 79 per cent, and glucosamine 21 per cent of the hexosamine. Since chondroitin sulfate contains nearly exclusively galactosamine as its hexosamine component (7), whereas hyaluronic acid contains only glucosamine, this finding indicates that the greater part of the isolated mucopolysaccharide material consists of chondroitin sulfate. The rather high mean sulfate value of 12.2 per cent supports this contention.

As seen from the data reported in the tables for the uronic acid content of the aortic mucopolysaccharides a good agreement was observed between the colorimetric and gasometric uronic acid analyses. Thus the average uronic acid concentration found by Dische's procedure was 33.3 per cent, as compared with a mean concentration of 33.4 per cent obtained by the modified Tracey method.

The consistently low protein values observed for the mucopolysaccharide material may be taken as a proof of the comparatively high purity of the samples. As mentioned previously, the absence of significant quantities of extraneous amino acids in the chromatograms performed on the acid hydrolysates of the mucopolysaccharide samples is in accord with the observed low protein content of the material.

No significant change with age was observed in the total hexosamine, uronic acid, sulfate, and protein content of the mucopolysaccharide samples. A difference was, however, noted in the amino sugar composition of the mucopolysaccharide samples for the 60-76 year group as compared with the other groups. Thus the galactosamine percentage of total hexosamine averaged 85, and the glucosamine percentage 15 for the samples from the 60 to 76 year group, as compared with 77 and 23 for samples from aortas of individuals aged 1 to 59 years. This difference is statistically significant ($t = 3.43$, $p < 0.01$).

TABLE 3. COMPOSITION OF ISOLATED AORTIC MUCOPOLYSACCHARIDES FROM INDIVIDUALS OF VARIOUS AGES.

Age Group (Yrs.)	Number of Samples	Total Hexosamine %	Galactosamine		Glucosamine		Uronic Acid %		SO_4 %	Protein %
			% of Hexosamine	R_f	% of Hexosamine	R_f	Colorimetric	Gasometric		
0-9	5	26.6	77	0.46	23	0.52	33.8	31.2	11.9	1.4
20-39	5	23.6	72	0.43	28	0.49	33.5	33.2	11.6	1.2
40-49	5	26.8	78	0.42	22	0.48	33.9	35.4	10.8	1.9
50-59	9	24.1	80	0.44	20	0.50	32.8	33.8	12.5	1.9
60-76	6	23.8	85	0.43	15	0.49	32.9	32.5	13.5	1.7
	Mean	24.8	79	0.44	21	0.50	33.3	33.4	12.2	1.6

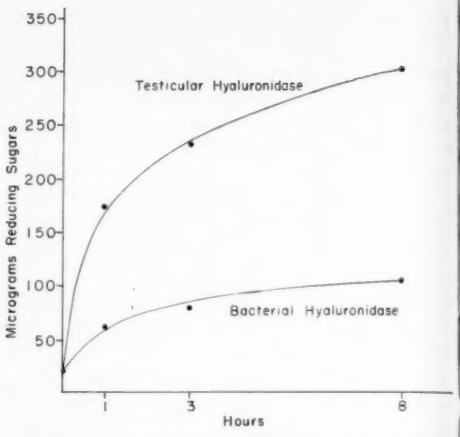

Fig. 4. Hydrolysis of arterial mucopolysaccharides by testicular and bacterial hyaluronidase. The values are expressed per 10 mg. of mucopolysaccharide material and represent the means of observations on 4 samples (No. 6, 9, 28, and 29, table 2).

The results of studies on the action of testicular and bacterial hyaluronidase on the arterial mucopolysaccharides are presented in figure 4. As seen from the figure the action of testicular hyaluronidase was found to be definitely greater than that of bacterial hyaluronidase. Since testicular hyaluronidase is capable of hydrolyzing chondroitin sulfate A and C (11) whereas staphylococcal hyaluronidase is without effect on chondroitin sulfate (1), this finding supports the assumption that an appreciable part of the mucopolysaccharides in the human aorta consists of chondroitin sulfate. The fact, however, that some hydrolysis of the mucopolysaccharide material was observed in the experiments with bacterial hyaluronidase suggests that hyaluronic acid or another compound susceptible to the action of bacterial hyaluronidase is also present in human aortic tissue.

SUMMARY

Determinations were made of the total hexosamine, galactosamine, glucosamine, uronic acid, acid-hydrolyzable sulfate, and protein content of 30 samples of mucopolysaccharides isolated from human aortic tissue obtained from individuals ranging in age between 1 and 76 years. The mean concentrations found were: total hexosamine, 24.8 per cent; uronic acid (colorimetric), 33.3 per cent; (gasometric), 33.4 per cent; sulfate (SO_4), 12.2 per cent; and protein, 1.6 per cent. Galactosamine averaged 79 per cent of the total hexosamine content, and glucosamine 21 per cent.

No certain variation with age was observed in the total hexosamine, uronic acid, sulfate, and protein content of the samples. Determinations of the amino sugar composition of the mucopolysaccharide material showed a higher galactosamine and a lower glucosamine content of samples derived from 60 to 76 year old subjects than of samples obtained from children and younger adults.

Testicular hyaluronidase was found to have a greater hydrolyzing effect on the arterial mucopolysaccharides than bacterial hyaluronidase.

The chemical analyses and enzyme studies indicate that chondroitin sulfate constitutes a greater part of the isolated mucopolysaccharides. The presence of other mucopolysaccharide compounds is, however, indicated by the finding of a notable quantity of glucosamine in the acid hydrolysates and by the demonstration of a definite, although small, effect of bacterial hyaluronidase on the mucopolysaccharide material.

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VITAMIN B_{12} SERUM CONCENTRATIONS IN 528 APPARENTLY HEALTHY HUMAN SUBJECTS OF AGES 12-94

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Although a few studies (4, 8, 13) have reported a gradual fall in average vitamin B_{12} levels in the serum with age, the number of subjects studied, particularly at the higher age levels, has not been large enough to permit a clear evaluation of the regression on age. It seems worth while, therefore, to present our results on several groups of subjects living under substantially different conditions.

MATERIALS AND METHODS

Subjects

Group A_1: These 89 subjects were ambulant, apparently healthy, males selected from patients of the Gerontology Branch and Infirmary Division of the Baltimore City Hospitals. Indications for admission were primarily socio-economic due to unemployability for reason of advanced age, rather than illness. All subjects had been inpatients and on the regular Hospital diet for at least one month and, in most cases, for several years. They were selected following a review of all available clinical information. Clinical observers found none to be acutely ill and no clear-cut reason for suspicion of other serious or debilitating illness. In no case had diagnosis of diabetes mellitus (6, 7), megaloblastic anemia, or leukemia (2, 3) been made. Diastolic blood pressure in excess of 120 mm. Hg had never been recorded in any of the subjects. No history was obtained of previous parenteral or oral administration of vitamin B_{12}, and there was no record of any B_{12} administration after admission.

The diet ingested by Baltimore City Gerontology Branch and Infirmary patients (on the Hospital regular diet) had previously been estimated during the course of metabolic balance studies to average daily: 1800 to 2000 calories, 9 to 12 Gm. nitrogen, 1.0 to 1.1 Gm. phosphorus 40 to 50 mEq. potassium, 200 to 250 Gm. carbohydrate, and 50 to 70 Gm. fat. B_{12} sources included meat or eggs (100 Gm./day) and milk (100 to 200 ml./day). It was believed that none of the subjects had unusual dietary patterns (for reasons of depressive states, absent or unsatisfactory dentures, vegetarian eccentricity, or the like).

Group A_2: These 55 subjects were physicians and other male staff members of the Gerontology Branch, the Baltimore City Hospitals, and the Johns Hopkins School of Hygiene and Public Health. Clinical histories were not obtained and physical examinations were not obtained on these subjects. All of them, however, were normally active in the performance of their usual duties.

Baltimore City Hospital interns and resident staff who participated in the study (11 of ages 20-29, 9 of ages 30-39, 2 of ages 40-49) lived in and received meals regularly at the Hospital. The Hospital diet made available to them was the same as that of the Gerontology Branch and Infirmary subjects. In either case, the diets may have been occasionally supplemented by sources outside the Hospital.

Diets of the Gerontology Branch and Johns Hopkins staff members were varied and uncontrolled. Dietary histories of a similar group (10) have shown intake of B_{12} in liberal amounts of milk, meat, cheese, etc. (12) to be 1 to 5 mγ (1×10^{-9} Gm.) per day.

Group B: These 97 volunteer subjects were ambulant, apparently healthy male inmates of a state penal institution in the same geographic region as Group A. All had been in the institution for at least 5 years prior to the test. During the latter period, all worked regularly in the prison shops and were offered the same diet prepared in the same kitchen. The diet was well-balanced and, with respect to adequacy of sources of B_{12}, included daily at

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least 0.18 Kg. of meat, an average of 0.8 egg and 100 ml. of milk in addition to the amounts of these used in cooking breads, desserts, etc.

Group C: These 96 male and 65 female subjects were made available by the Commission on Chronic Illness Survey and the Johns Hopkins School of Hygiene and Public Health (9). They were part of a study designed to evaluate nature and extent of disease in the Baltimore population at large, detectable by certain screening procedures including history, physical examination, blood and urine analysis, liver function tests, and x-ray study of the gastrointestinal tract. The 161 subjects were among those who presented themselves for examination in response to an invitation which was offered to a probability sample of the population of Baltimore. As the refusal rate was high (41 per cent), the subjects are not strictly representative of Baltimore residents. They are, however, considered to be a fair cross-section of the population. As such, they are quite heterogeneous with respect to many variables such as race, socio-economic group, diet, etc. With respect to these variables, it would seem unlikely that subjects in any age group were substantially different from those of any other age group.

Group D: These 82 male and 44 female subjects were ambulant, apparently healthy residents of a private home for the aged in New York City. The younger subjects were employees of the home who lived in the home and subsisted on the same well-balanced institutional diet as the older subjects. Diet of both staff members and patients may have been supplemented by occasional meals outside the home. Except for the employees, the residents of the home are drawn primarily from higher socio-economic levels.

Experimental Design

Procedure. Blood specimens on all subjects were obtained in fasting state and without use of anticoagulant in the early morning (6:00 a. m. to 8:30 a. m.). Most of these were obtained in the interval from January through June, 1956, although some of the specimens on subjects in Groups B, C, and D were drawn and analyzed during the preceding year. Sera were separated into tubes identified only by code number and stored in frozen state until assayed at the School of Hygiene and Public Health.

Analytic Method. Two ml. of serum were added to a tube containing 8.0 ml. of acetate buffer, pH 4.6. The tube was covered snugly with a piece of aluminum foil and heated in a boiling water bath for 30 minutes. After cooling with cold water, tubes were centrifuged and 6 ml. of clear supernatant fluid were removed and neutralized with 1 ml. of Na_2HPO_4 (0.33 molar); 1.0, 2.0 and 3.0 ml. of this mixture were then assayed for microbiologic activity of B_{12} according to Skeggs and associates (17).

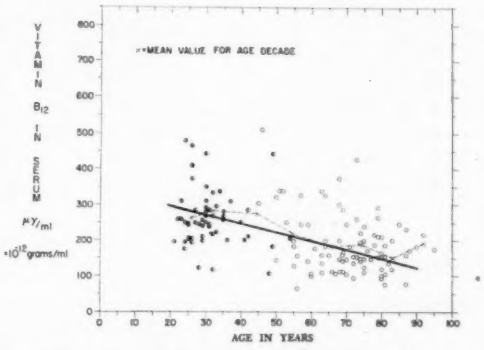

Figure 1. B_{12} levels of apparently healthy subjects in Group A_1 (Baltimore City Gerontology Branch and Infirmary) and Group A_2 (staff of the Gerontology Branch, Baltimore City Hospitals and the Johns Hopkins School of Hygiene and Public Health).

○ = Group A_1
◐ = Group A_2, BCH staff
◑ = Group A_2, JHSHPH staff

Regression line shown is unweighted average for Groups A_1, B, and C.

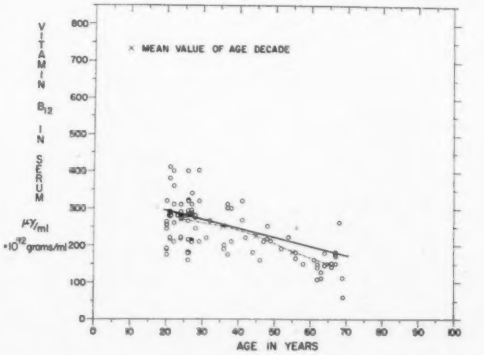

Figure 2. B_{12} levels of subjects in Group B (apparently healthy subjects who had lived under comparable conditions for more than 5 years in a state penal institution.) Regression line shown is unweighted average for Groups A_1, B, and C.

RESULTS

In figures 1-4, the individual values and mean serum B_{12} for each decade of age are given for each of the groups studied. For each of the groups, almost uniform gradual decline in mean serum values was noted with advancing age.

A broad spread of ages was available in each of the groups A_1, B, and C, and all of the subjects in each of these groups were drawn from distinct populations. In table 1 is given, for each of the groups A_1, B, and C and the combined group $A_1 + B + C$, an estimate of the mean serum B_{12} level at a standard age, 50 year ($Est._{50}$), in order to make possible comparison of the groups despite differences in the mean age ($\bar{x}$) of the subjects in the groups. Also in table 1 is given, for each of the groups, the standard deviation about the regression line, ($S_{y,x}$), the slope of the regression line (b), the standard error of the slope (S_b), and the level of statistical significance for the regression on age (P). The estimates of the B_{12} level at the standard age, 50 years, were not significantly different for Group A_1, B, and C: 237, 198, and 218 $\mu\gamma$/ml. with standard deviations about the regression lines of 78.2, 54.6, and 91.5 $\mu\gamma$/ml., respectively. The regression appeared to be substantially linear over the entire range of ages from 20 to 90. Slopes of regression of B_{12} levels on age were not significantly different for the three groups (-23.5, -29.1, -21.5 $\mu\gamma$/ml. decade, respectively, with standard deviations of the slope of 7.5, 3.4, and 5.1 $\mu\gamma$/ml. decade, respectively).

The unweighted average estimate of B_{12} level at age 50 (218 $\mu\gamma$/ml.) and unweighted average slope of regression on age (24.7 $\mu\gamma$/ml.

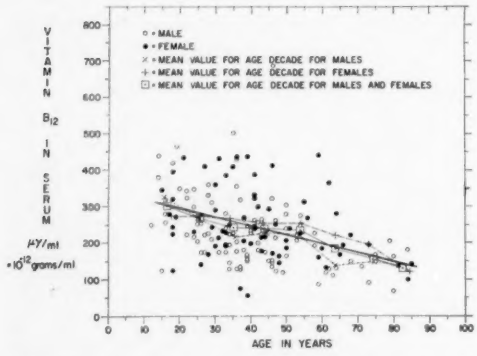
VITAMIN B12 IN SERUM
μγ/ml
•10^12 grams/ml
○ = MALE
● = FEMALE
× = MEAN VALUE FOR AGE DECADE FOR MALES
+ = MEAN VALUE FOR AGE DECADE FOR FEMALES
⊡ = MEAN VALUE FOR AGE DECADE FOR MALES AND FEMALES
AGE IN YEARS

Figure 3. B_{12} levels in a probability sample of the Baltimore population. Regression line shown is unweighted average for Groups A_1, B, and C.

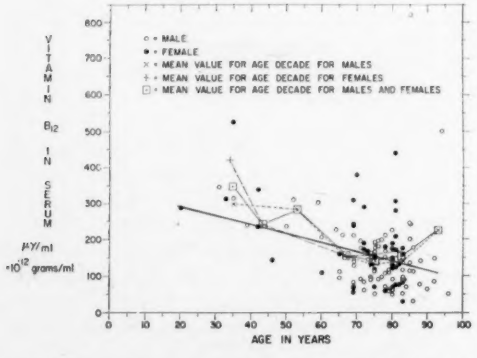
VITAMIN B12 IN SERUM
μγ/ml
•10^12 grams/ml
○ = MALE
● = FEMALE
× = MEAN VALUE FOR AGE DECADE FOR MALES
+ = MEAN VALUE FOR AGE DECADE FOR FEMALES
⊡ = MEAN VALUE FOR AGE DECADE FOR MALES AND FEMALES
AGE IN YEARS

Figure 4. B_{12} levels in staff (younger subjects) and apparently healthy residents (older subjects) in a private home for the aged in New York City. Regression line shown is unweighted average for Groups A_1, B, and C.

TABLE 1. REGRESSIONS OF SERUM B_{12} LEVELS ON AGE (FOR AGES $\geq$ 20).

Variable		Units	GROUP			
			A_1	B	C	A_1+B+C
Number of Subjects.....	N		89	97	144‡	330
Average Age...	$\bar{x}$	Years	70.7	36.0	44.0	48.8
Estimate of B_{12} Level at Age 50	$Est._{50}$	1×10^{-12} Gm./ml.	237	198	218	222*
Standard Deviation About Regression Line	$S_{y.x}$	1×10^{-12} Gm./ml.	78.2	54.6	91.5	79.0
Slope of Regression on Age...	b	1×10^{-12} Gm./ml. /decade	−23.5	−29.1	−21.5	−20.*†
Standard Error of b.....	S_b	1×10^{-12} Gm./ml. /decade	7.5	3.4	5.1	2.2
Level of Statistical Significance.....	P		<0.001	<0.001	<0.001	<0.001

* In plotting regression line on figures 1-4, the unweighted average for the 3 Groups A_1, B, and C was used ($Est._{50}$ = 218 $\mu\gamma$/ml.; b = −24.7 $\mu\gamma$/ml. decade).

† Lower than value for Group A_1, B, or C in consequence of differences in age distribution of the groups.

‡ The remainder of the 161 subjects in this group were of ages 12-19 and were not considered in calculation of regression.

decade) were used to determine the regression line drawn on each of the figures 1-4. It is apparent from figure 1 and 4 and table 2, however, that the scatter of the points for the physicians and other staff members in Group A_2 and for the staff and patients in Group D agree well with the average regression line for Groups A_1, B, and C. As seen in figures 3 and 4, there seems to be no substantial difference between the B_{12} levels of males and those of females.

It is remarkable that, despite the differences in the populations represented by Group A_1, B, and C, the regression lines for these groups are nearly identical. This agreement, together with the agreement in scatter of values for Groups A_2 and D about the average regression line for Group A_1, B, and C, is suggestive that, unlike many other vitamins, B_{12} serum levels vary with age but not to any large extent with socio-economic or dietary factors. Yet, it still might be expected that degree of homogeneity in the various groups would be reflected to some small extent in the variability of values about the regression line. Thus, it would not be surprising if the greater uniformity in living conditions over a period of at least 5 years in the case of the prisoner population resulted, compared to other groups, in smaller individual differences in the scatter of values about the regression line. Such is the case: for Group B, the standard deviation about the regression line is significantly smaller than for any of the other groups for which it was calculated (54.6 $\mu\gamma$/ml.).

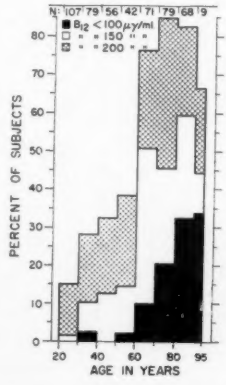

Figure 5. Incidence of low B_{12} levels in 511 apparently healthy human subjects of ages 20-94.

TABLE 2. SERUM B_{12} LEVELS FOR APPARENTLY HEALTHY ADULT MALE BALTIMORE CITY HOSPITALS AND JOHNS HOPKINS STAFF MEMBERS (GROUP A_2) AND STAFF AND RESIDENTS IN A PRIVATE HOME FOR THE AGED IN NEW YORK (GROUP D).

Variable		Units	GROUP	
			A_2	D
Number of Subjects..	N		55	126
Average Age.....	$\bar{x}$	Years	30.6	74.1
Average B_{12}.....	$\bar{y}$	1×10^{-12} Gm./ml.	268.0	165.4
Standard Deviation of the Distribution..	s	1×10^{-12} Gm./ml.	81.3	113.0

The regression of B_{12} levels on age for ages $\geqq 20$ was statistically significant ($P < 0.001$) for each of the groups and the combined group. In computing regression of serum B_{12} level on age, data on subjects of ages less than 20 have been disregarded to minimize possible influences due to growth.

Incidences of low serum B_{12} values in various age decades are given in figure 5. Immediately apparent is the increase in the percentage of subjects having lower serum B_{12} concentrations among individuals over 50 years of age; this is true for all B_{12} levels considered (< 100, < 150, < 200 $\mu\gamma$/ml.). Comparison of 20-49 year with 50-94 year age groups revealed the percentage incidence of values < 100 $\mu\gamma$/ml. in the younger group of 0.83 per cent compared to 18.2 per cent in the older group (32.4 per cent for subjects 80-89 years of age). For levels < 150 $\mu\gamma$/ml. and < 200 $\mu\gamma$/ml., the values compared in the same direction were 7.02 per cent versus 45.4 per cent and 23.2 per cent versus 74.0 per cent, respectively.

DISCUSSION

Reliability of Methods. Pooled sera, preserved in frozen state and analyzed with each assay group, showed no systematic trend during the interval in which analyses were performed (fig. 6). Microbiologic and radioactivity assay on specimens of pooled sera from young adult subjects and pooled sera from elderly subjects, to which varying amounts of cobalt^{60}-labelled vitamin B_{12} had been added, demonstrated sat-

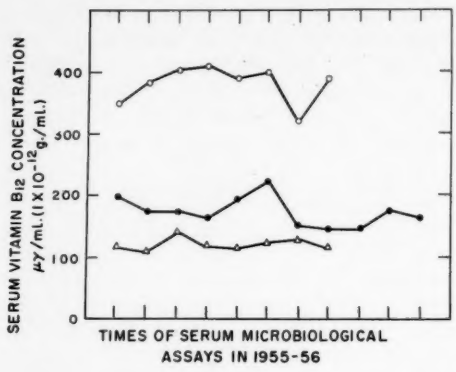

Figure 6. Vitamin B_{12} assay values obtained on pooled sera specimens analyzed with each group of microbiologic assays in 1955-56.

○ = specimen of pooled sera from healthy young adult humans

△ = specimen of pooled sera from healthy old adult humans

● = specimen of pooled sera from healthy adult humans

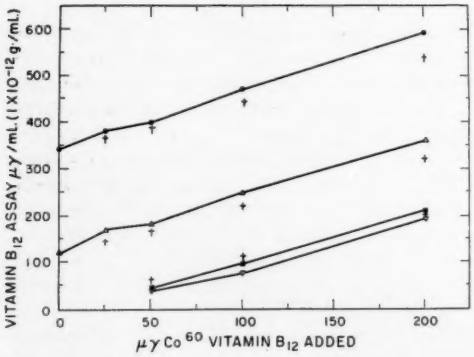

Figure 7. Actual and theoretic microbiologic and radioactivity assay values for two pooled sera following addition of 25, 50, 100, and 200 $\mu\gamma$ of cobalt ^{60}-labelled vitamin B_{12}.

● = pooled sera from young subjects. Microbiologic assay

△ = pooled sera from old subjects. Microbiologic assay

■ = pooled sera from young subjects. Radioactivity assay

▽ = pooled sera from old subjects. Radioactivity assay

+ = theoretic assay values

isfactory recoveries (fig. 7). The latter results make it unlikely that microbiologic inhibition, of whatever nature, may be present in larger quantities in the sera of the older patients, or that factors which can replace B_{12} in growth of the organism *Lactobacillus leichmannii* 4797 are present in larger quantities in the sera of younger subjects. It would seem quite unlikely, although not entirely ruled out, that more B_{12} bound to protein is lost, in the analytic procedure, from sera of old subjects compared to that of young adults. This possibility would seem all the more unlikely in view of the downward trend of B_{12} values with advancing age observed by Boger and associates (4) in 3 out of 4 of the groups in their study using a method which they believe minimizes losses of protein-bound B_{12}.

TABLE 3. RESULTS OBTAINED IN AGE-WISE STUDIES OF SERUM VITAMIN B_{12} LEVELS IN HEALTHY HUMAN SUBJECTS OF AGES ≧ 20.

Reference	Age (Years)		N	Serum B_{12} Concentration		Regression Coefficient (1×10^{-12} Gm./ml,yr.)	Level of Significance P
	Range	Mean		Mean	S.E.		
Mollin and Ross (13).....	15-40		65	358	16.1		
	51-70		27	322	28.9		
	71-93		31	259	31.6		
Chow *et al.* (8)...	21-40	29.5	17*	231.5	27.6		
	19-28	23.2	48*	268.2	16.5		
	70-90	77.2	13	153.4	18.4		
	68-89	75.4	26*	151.8	18.7*		
	66-92	78.2	93*	147.7	8.9		
	58-75	66.0	3	180.5	25.2		
	10-19		10*	284.0	31.9		
	20-29		19*	249.3	16.5		
	30-39		33*	235.3	19.3		
	40-49		31*	239.6	20.0		
	50-59		10*	210.2	20.6		
	60-69		6*	213.8	40.2		
	70+		5*	89.6	13.0		
Boger *et al.* (4)...	14-87	42	108	580			
	14-94	59	238	570		−2.2	<0.05
	8-87	37	41	700		−5.2	<0.001
	21-54	32	141	510		−4.8	<0.01
Present Study.... (Total Group)	20-29	24.7	107	269.8	6.88	−2.2	<0.001
	30-39	34.3	79	259.5	10.83		
	40-49	44.2	56	242.9	13.64		
	50-59	54.3	42	226.6	11.58		
	60-69	65.5	71	166.8	8.45		
	70-79	74.8	79	157.6	7.57		
	80-89	82.7	68	149.9	17.61		
	20-89	52.4	502	213.1	4.43		

* Included in present study also.

Individual Variation. The existence of large individual differences, apparent for all age groups, has previously been described for age-wise (4) and other serum B_{12} studies (2, 15, 16).

Comparison of Results with Those of Other Studies. The values in table 3 are presented to facilitate comparison of the results of the present study with those from previous age-wise studies.

Mollin and Ross (13) noted lower vitamin B_{12} serum levels in old as compared to young subjects. Sixty-five apparently normal doctors, nurses, and technicians of ages 15 to 40 had a mean serum B_{12} concentration of 358 $\pm$ standard error of the mean of 16.1 $\mu\gamma$/ml. (range 100 to 720 $\mu\gamma$/ml.). Two "older, poorer, and less well cared for" groups of "healthy subjects with minor complaints" were studied. Many of the latter had "disabilities common to their age group, but none was seriously ill or anemic." Thirty-one of these subjects, ages 51 to 70, had a mean B_{12} serum concentration of 322 $\pm$ 28.9 (range 110 to 620 $\mu\gamma$/ml.), not significantly different from the younger group. Thirty-one subjects of ages 71 to 93, however, had a mean value of 259 $\pm$ 31.6 (range 60 to 600 $\mu\gamma$/ml.), significantly lower than for the group of ages 15 to 40 ($P < 0.001$). Chow and associates (8) observed B_{12} serum levels of 65 young adults from 2 institutions to be significantly higher than those of 145 old subjects from 4 institutions. The latter paper also reported downward age-wise trend in mean values of serum B_{12} levels grouped by decades of age for 145 individuals screened as clinically healthy after random selection from the Baltimore population at large. A study of 528 males and females in 4 groups by Boger and associates (4) revealed significant regressions in 3 of the groups while the remaining, composed of 108 apparently normal males at Norristown State Hospital showed no regression on age.

Sources of Age-Wise Bias in Results

Subject Selection. Criteria of selection have been chosen in an attempt to eliminate subjects with illness or relevant disease. Criteria related to health status constitute the only known selection introduced into the group screened from the probability sample of the Baltimore population (Group C). Yet, in this group, as in the others, regression on age was highly significant. This strengthens the view that the factors responsible for regression of B_{12} levels on age in the apparently healthy institutionalized populations are also present with similar effectiveness in the healthy population at large.

Diet. Results obtained in animal studies by others (5, 11) have indicated that B_{12} level is influenced by composition of the diet. Our own studies in the human indicate that regression of B_{12} level on age is present even when dietary differences are solely those due to selection from an adequate diet by the subjects themselves. This observation, made for the subjects of Group B, is confirmed by the results for Group A.

The agreement in values between the several groups within a decade of age and the observed decrease with advancing age in each group, under the diverse conditions holding for the several groups, indicates that the serum B_{12} is relatively unaffected by these conditions and that the observed decrement in B_{12} level is age dependent. It would seem that if dietary conditions per se play a significant role in the age-wise decrease of serum B_{12} in the groups studied, they do so in consequence to an age-dependent alteration in the selection of foods by the subjects themselves.

Clinical Significance of Lower Serum B_{12} in the Aged. Regardless of what reasonable value (in the light of existing information) is selected as a level below which a B_{12} deficiency state is likely to exist, a higher percentage of older people, compared to younger adults, have such serum B_{12} concentrations. Minimum normal level of B_{12} in serum has been accepted by several investigators (1, 13, 14) as about 100 $\mu\gamma$/ml.

SUMMARY AND CONCLUSIONS

1. Assays of vitamin B_{12} (cyanocobalamin, or derivative) concentration by growth responses of *Lactobacillus leichmannii* have been made in fasting serum specimens from 528 persons of ages 12-94, of whom 419 were males, all believed free of relevant disease, obtained from 3 institutions and by random sampling from the Baltimore population at large.

2. Regression of serum B_{12} level on age was highly significant ($P < 0.001$) for each of the groups. For groups in which there was a broad spread of ages (a public home for the aged, a penal instution, and a probability sample of the city of Baltimore), estimated values at age 50 were 237, 198, and 218 $\mu\gamma$/ml., respectively

(unweighted average of 218 $\mu\gamma$/ml.), with standard deviations about the regression lines of 78.2, 54.6, and 91.5 $\mu\gamma$/ml., respectively. Slopes of regression on age were −23.5, −29.1, and −21.5 $\mu\gamma$/ml. decade, respectively, with standard errors of 7.5, 3.4, and 5.1 $\mu\gamma$/ml. decade, respectively. Scatter of values from physicians and other staff at the public home for the aged, and staff and patients at a private home for the aged, agreed well with the unweighted average regression line (estimated B_{12} level at age 50: 218 $\mu\gamma$/ml., regression slope 24.7 $\mu\gamma$/ml. decade) calculated for the more homogeneous groups.

3. Comparison of 20-49 year with 50-94 year age groups revealed the percentage incidence of values < 100 $\mu\gamma$/ml. in the younger group of 0.83 per cent compared to 18.2 per cent in the older group (32.4 per cent for subjects 80-89 years of age). For levels < 150 $\mu\gamma$/ml. and < 200 $\mu\gamma$/ml., the values compared in the same direction were 7.02 per cent versus 45.4 per cent and 23.2 per cent versus 74.0 per cent, respectively.

4. Available evidence supports the contention that observed regression of serum B_{12} levels on age is statistically significant. The agreement in regression lines between the several groups, widely different in background and living conditions, suggests that the B_{12} level is relatively unaffected by these conditions. If dietary conditions per se play a significant role in the age-wise decrease in serum B_{12} in the groups studied, they do so in consequence of an age-dependent alteration in the selection of foods by the subjects themselves.

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THE VITAMIN C NUTRITIONAL STATUS AND CAPILLARY FRAGILITY IN CHRONIC MENTAL PATENTS

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The vitamin C nutritional status and capillary fragility have been determined in a group of mental patients domiciled in this institution. The relation of vitamin C to the health and strength of the capillary has been long recognized but vaguely understood. From his long study of the genesis of atherosclerosis in the group of patients from which our smaller group was drawn, Paterson (12) has suggested that intimal capillaries may rupture because of weakness in the capillary endothelium. This would permit the deposition of blood and blood products (including cholesterol) and the formation of atherosclerotic plaques in the arterial intima. Willis (17) has produced atherosclerosis in guinea pigs by feeding them a scorbutic diet. It has been considered that vitamins C and P are essential to the maintenance of normal ground substance (3, 14, 15, 18). In hypovitaminosis C, perhaps accompanied by vitamin P deficiency (11), there is depolymerization of the glycoprotein ground substance with weakening of the capillary (3).

The association between the state of vitamin C nutrition and capillary fragility was first observed in 1914 by Hess and Fish (5), who found markedly increased capillary fragility in cases of frank scurvy. Non-scorbutic vitamin C deficiency may contribute to decreased capillary strength. In theory then, administration of ascorbic acid and vitamin P should restore capillary strength. The results of various studies, including our own, do not confirm this. Indeed, Scarborough (16) has found no correlation between the plasma vitamin C values, the results of saturation tests, and the degrees of capillary fragility; further, he has not observed an increase in capillary strength by ascorbic acid administration in non-scorbutic deficiency states.

MATERIAL AND METHODS

The studies were carried out on white male mental patients, domiciled in the hospital for several years. None were acutely disturbed nor receiving shock therapy. Thirty-eight of these patients were in an older age group (64 ± 9 years) and 8 were in a younger age group (34 ± 3 years). Clinical data are given in table 1.

The patients were all consuming the usual hospital diet, which contained on calculation an average of 80 mg. of ascorbic acid per day. Fasting blood determinations of ascorbic acid were made on three occasions: Control; 24 hr. after 100 mg. ascorbic acid by mouth; and 24 hr. after 1000 mg. ascorbic acid by mouth. The 24 hr. urinary excretion of vitamin C was determined under control conditions and after both of the doses of ascorbic acid. The last two urinary determinations were part of a vitamin C saturation test (1, 4, 19). According to this test, tissue deficiency of ascorbic acid is indicated if the 24 hr. excretion is less than 50 per cent of the 100 and 1000 mg. doses. Whole blood and urine ascorbic acid values were determined by the method of Roe and Keuther (13). This analysis includes the measurement of both ascorbic and dehydroascorbic acid.

Capillary fragility was measured, in the control state and after the 1000 mg. ascorbic acid administration, by the negative pressure method of Hines and Parker (6). A petechiometer* calibrated at 100, 200, and 300 mm. Hg negative pressure was applied to the interscapular area of the skin for 1 minute at each pressure level, and the number of petechiae produced within a 2 cm. circular area were counted. Results were interpreted as follows:

negative (less than 10 petechiae at —300 mm. Hg calibration)
1 (10 or more petechiae at —300 mm. Hg calibration but less than 10 at —200 mm. Hg calibration)
2 (10 or more petechiae at —200 mm. Hg calibration but less than 10 at —100 mm. Hg calibration)
3 (10 or more petechiae at —100 mm. Hg calibration but no gross ecchymosis)
4 (gross ecchymosis)

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* Rexall Company.

TABLE 1. CLINICAL DATA.

Group	Number of Patients in Group	Average Age Per Group	Diagnoses			Average Platelet Count/Group		Treatment per Day
			Mental Disease	Diabetes Mellitus	Essential Hypertension	Pre-Treatment	Treatment	
A	10	67	Schizophrenia – 7 Manic Depressive – 1 Involutional Melancholia – 1 Psycho-neurosis – 1	1	3	159,400	181,700	Ascorbic Acid 100 mg.
B	10	63	Schizophrenia – 5 Psychosis with Epilepsy – 2 Manic Depressive – 1 Psychosis with Cerebral Arteriosclerosis – 1 Post Traumatic Psychosis – 1	0	1	139,600	195,700	Vitamin P (Rutin) 100 mg.
C	9	62	Schizophrenia – 4 General Paresis – 1 Senile Dementia – 1 Psychosis with Epilepsy – 1 Alcoholic Psychosis – 1 Sociopathic Personality – 1	2	0	151,700	159,700	Ascorbic Acid 100 mg. Vitamin P (Rutin) 100 mg.
D	9	63	Schizophrenia – 7 Maniac Depressive – 1 Mental Deficiency – 1	0	4	166,500	170,890	Orange Juice 200 ml.
E	8	34	Schizophrenia – 7 Post-traumatic Psychosis – 1	0	0	145,375	187,600	Ascorbic Acid 100 mg. Vitamin P (Rutin) 100 mg.

Thrombocytopenia was not present in any of the subjects. Other conditions present in the group which may increase capillary fragility are noted in table 1 (hypertension, 8 cases, diabetes mellitus, 3 cases).

Two methods of measuring capillary strength are available—the positive and negative pressure techniques. The accuracy of either method is questionable (10). We chose the negative pressure technique, a modification of the Da Silvo Mello method by Hines and Parker (6), because of its greater accuracy. Further studies were performed in this laboratory to confirm this conclusion. The critical pressure of capillary rupture was measured in 15 young normal individuals employed in the hospital, using a modification of the Da Silvo Mello apparatus. Constant negative pressure was created in a plastic suction cup 2 cm. in diameter by an electric aspiration pump. The system was connected to a Hg manometer to measure pressure; the pressure was kept constant by an air inlet valve on the aspiration pump. The suction cup was applied to the skin of 6 areas of the back, 3 on each side of the vertebral column. The 3 areas were 2, 4, and 6 in., respectively, below the spine of the seventh cervical vertebra. They are designated 1, 2, and 3, right and left, in table 2. The critical pressure of capillary rupture was taken as that amount of negative pressure which, when applied for one minute, would produce 1 petechia in the area 1 cm. in diameter in the center of the 2 cm. diameter area of application of negative pressure. The results of these studies are shown in table 2, and it can be seen that the maximum variation of critical pressure in any individual was 150 mm. Hg. This rather large variation in the range of critical pressure is moderately well taken into account in Hines and Parker's (6) method of expression of capillary strength. We considered this test to be the most satisfactory of those available.

Following completion of the preliminary investigation, the series was divided into 5 groups, A, B, C, D, and E. The last group consisted of the young individuals. These groups were placed on the various ascorbic acid and Rutin (vitamin

TABLE 2. CAPILLARY FRAGILITY IN YOUNG NORMAL INDIVIDUALS. CRITICAL PRESSURE OF CAPILLARY RUPTURE IN MM. HG NEGATIVE PRESSURE.

Subject	Sex	Age	Areas of Back (See Text)					
			Right			Left		
			(1)	(2)	(3)	(1)	(2)	(3)
A. R.	M	30	500	500	400	400	400	500
S. P.	F	28	150	300	250	300	150	150
A. H.	F	26	50	50	50	120	150	100
E. C.	F	27	80	50	100	120	50	50
V. T.	F	34	200	200	100	250	100	100
D. M.	F	21	300	300	400	300	250	400
E. H.	F	22	250	300	300	350	400	300
P. H.	F	30	150	200	200	150	200	200
M. Mc.	F	32	100	50	100	50	50	50
D. B.	F	36	50	50	50	50	100	50
M. V. B.	F	30	50	50	50	50	50	50
G. G.	F	26	50	50	50	50	50	50
W. F.	M	39	50	50	50	50	50	50
W. W.	M	31	200	100	200	250	100	150
J. M.	F	37	50	100	100	50	100	100

P) intakes outlined in table 1 for a period of 10 weeks. Analysis of 200 ml. of orange juice showed an average content of 92 mg. of vitamin C. In addition, it was believed that orange juice gave a high intake of vitamin P (16). At the conclusion of this period, the whole blood values and 24 hr. urinary vitamin C values and the capillary fragilities were again determined.

RESULTS

Blood ascorbic acid values are shown in table 3. The normal fasting whole blood level of ascorbic acid and dehydroascorbic acid is 0.8 mg. per cent (1). It can be seen that all groups showed a control blood level lower than normal. The higher value in the young age group (E) was not significantly different from the average of the 4 older age groups (ABCD).

The 100 mg. dose of vitamin C did not raise the blood level significantly in any group. The 1000 mg. dose, however, produced a significant elevation which placed the blood ascorbic acid of each group within the normal range. After 10 weeks on the various regimes, the blood ascorbic acid was within normal range in all groups with the exception of B, which received only vitamin P. The administration of synthetic vitamin C alone (group A) produced a significantly higher blood level than administration of synthetic vitamins C plus P (group C) or administration of naturally occurring vitamins C plus P (group D) (orange juice).

TABLE 3. AVERAGE BLOOD ASCORBIC ACID VALUES PER GROUP.

Group	Control		24 hr. After 100 mg. Vitamin C	24 hr. After 1000 mg. Vitamin C		After 10 Weeks' Treatment	
	mg./ 100 ml. ± SEM	P Value Groups ABCD to E	mg./ 100 ml. ± SEM	mg./ 100 ml. ± SEM	P Value to Control	mg./ 100 ml. ± SEM	P Value to Group A
A	0.44±.068		0.56±.069	1.12±.162	<.01	1.23±.065	
B	0.39±.041		0.46±.047	0.99±.097	<.001	0.44±.033	
C	0.43±.073		0.55±.081	0.94±.139	<.01	0.85±.058	<.01
D	0.51±.061		0.57±.064	1.01±.122	<.01	0.95±.032	<.01
ABCD	0.44±.050						
		>.05					
E	0.65±.097		0.61±.086	1.06±.089	<.01	0.96±.109	

The vitamin C saturation test (table 4) showed that all groups had tissue undersaturation of ascorbic acid for they all failed to excrete 50 per cent or more of both the 100 and 1000 mg. doses of vitamin C. The higher urinary excretion of vitamin C in the younger age group (E) was not significantly different from the average of the older age groups (ABCD). After 10 weeks' treatment, groups A, C, and E showed a urinary ascorbic acid excretion greater than 50 per cent of the daily intake but groups B and D (Vitamin P and orange juice) did not.

Table 5 shows the results of the capillary fragility studies. With the exception of group B, in which there was some reduction of capillary fragility after 1000 mg. of vitamin C, no

TABLE 4. VITAMIN C SATURATION TEST PER GROUP. AVERAGE URINARY VITAMIN C. MG./24 HOURS.

Group	Control	After 100 mg. Vitamin C		After 1000 mg. Vitamin C		After 10 Weeks' Treatment
	mg./ 24 Hr. ±SEM	mg./ 24 Hr. ±SEM	P Value Groups ABCD to E	mg./ 24 Hr. ±SEM	P Value Groups ABCD to E	mg./ 24 Hr. ±SEM
A	9.2±1.70	10.9±1.46		80.9±32.31		73.8±8.07
B	16.3±2.07	16.2±2.33		145.9±53.85		17.5±2.45
C	19.4±4.07	23.3±6.38		190.4±45.06		61.5±9.35
D	21.9±2.89	26.6±4.50		117.1±43.93		33.9±2.79
ABCD		19.3±7.06		133.6±42.26		
			>.05		>.05	
E	19.8±2.43	32.8±9.50		221.4±65.35		61.2±10.03

TABLE 5. AVERAGE CAPILLARY FRAGILITY PER GROUP.

Group	Control ± SEM	After 1000 mg. Vitamin C ± SEM	After 10 Weeks' Treatment ± SEM
A	3 ± 0.2	3 ± 0.2	3 ± 0.2
B	3 ± 0.3	2 ± 0.4	3 ± 0.2
C	3 ± 0.4	3 ± 0.4	3 ± 0.2
D	3 ± 0.3	3 ± 0.2	3 ± 0.4
E	3 ± 0.5	3 ± 0.5	3 ± 0.5

significant effect was produced on capillary fragility either by the 1000 mg. of vitamin C or the 10 weeks of treatment.

DISCUSSION

The presence of non-scorbutic hypovitaminosis C in institutionalized aged persons has been observed by Kirk and Chieffi (7, 8, 9), who found a progressive decline in the blood ascorbic acid with age. Oral administration of ascorbic acid produced normal blood levels in all but 3 subjects, and in these 3, normal levels were produced with parenteral administration of vitamin C. Kirk and Chieffi have therefore postulated that there is decreased absorption of vitamin C caused by its destruction in the intestinal tract. Cass and associates (2) have also observed non-scorbutic hypovitaminosis C in elderly institutionalized patients. The blood ascorbic acid was raised to 1.53 mg. per cent with orange juice, and a higher level of 2 mg. per cent was produced with 4 Gm. of ascorbic acid daily. However, after 4 months of treatment, there was a fall in the blood level in both groups to 0.94 mg. per cent.

The results of our studies are similar to those of Kirk and Chieffi and Cass and associates. Our institutionalized chronic mental patients had non-scorbutic hypovitaminosis C despite an adequate supply on the usual hospital diet. The ascorbic acid deficiency state is shown by the low blood ascorbic acid and the failure to excrete 50 per cent or more of the 100 and 1000 mg. doses in the saturation tests. We were unable to explain the hypovitaminosis C in our younger age group. The ascorbic acid deficiency state was associated with decreased capillary strength in all groups. However, the various therapeutic regimes, although improving the state of vitamin C nutrition, failed to change capillary strength. These observations are in agreement with those of Scarborough (16) and show no correlation between the degree of capillary strength, the blood ascorbic acid, and the results of a saturation test.

Our results, however, offer an interesting opportunity for speculation as to the role of vitamin P and other unknown substances in orange juice that may increase tissue uptake of ascorbic acid. After 10 weeks of therapy, the groups receiving synthetic vitamin C with or without vitamin P excreted 50 per cent or more of the dose. There was greater excretion with vitamin C alone than with vitamin C and P combined. In the group receiving these substances in their naturally occurring form (orange juice), the excretion was only 36.8 per cent, despite a blood level that was within normal range. It is hypothesized that administration of vitamin C to patients with non-scorbutic deficiency states first elevates the blood level to normal. Following this, the ascorbic acid is taken up by the tissues until they are fully saturated. When this occurs, further administration leads to increased urinary excretion as both blood and tissues are saturated. In group D the low urinary output would indicate that tissue uptake of vitamin C was still occurring after the 10 weeks' therapy. The urinary excretion was lower in group C than in group A. Vitamin P may, therefore, enable greater tissue uptake of vitamin C. Other unknown substances may be present in orange juice which increase tissue uptake of vitamin C even more than vitamin P.

SUMMARY

The state of vitamin C nutrition and capillary fragility have been determined in groups of permanently hospitalized psychiatric patients. Low plasma ascorbic acid values, tissue vitamin C undersaturation, and increased capillary fragility were observed, despite an adequate dietary intake of vitamin C. There was no difference between the degree of this vitamin C deficiency state in the older and younger age groups. No increase in capillary strength was produced by 1000 mg. of ascorbic acid or by 10 weeks' therapy with ascorbic acid, vitamin P (Rutin), both these materials combined, or orange juice. There was no correlation between the degree of vitamin C deficiency and the degree of capillary fragility. Treatment raised significantly the blood ascorbic acid values. It would seem that tissue uptake of vitamin C is enhanced by vitamin P (Rutin) and to an even greater degree by unknown substances present in orange juice.

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EFFECT OF AGE ON THE LIPEMIA CLEARING ACTIVITY OF SERUM AFTER ADMINISTRATION OF HEPARIN TO HUMAN SUBJECTS

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The clearing factor is a thermolabile active principle produced in vivo on the administration of heparin or some related substances (2, 12, 30). It causes, in vivo and in vitro, a rapid clearing of protein-containing neutral fat emulsions, such as alimentary lipemic plasma. Studies on the mechanism of this action have demonstrated beyond doubt that the clearing phenomenon involves a splitting of neutral fat to fatty acids and glycerol with subsequent solubilization of the former by its binding to albumin (9, 23, 27) and to beta lipoprotein (23). Apparently only protein-bound triglycerides are available as substrate, the clearing factor thus being a lipoprotein lipase (19). Its action on lipemic or fasting plasma is accompanied by a marked decrease or total disappearance of the neutral fat-carrying particles, the chylomicra and the lighter molecules of the beta lipoprotein group (S_f 20-400 in Gofman's nomenclature) with a concomitant increase of the main beta lipoprotein and the high density lipoproteins (5, 10, 20). The recent development of an effective purification procedure for the enzyme from postheparin plasma (24), probably permits a still further characterization of the participants in, and the mechanism of, the clearing reaction.

The possible physiologic role of the clearing factor in fat metabolism has become a subject of great interest. The presence in plasma of a clearing factor of endogenous origin was suggested by the demonstration of the lipemia-increasing effect of protamine (6, 29) and toluidine blue (15) and it has since then been detected in small amounts in human plasma (7, 8, 22) and in considerable quantities in rat plasma during fat absorption (17). Through the demonstration of a heparin-activated lipoprotein-specific lipase with clearing factor-like properties in normal heart tissue of the rat, Korn (18, 19) has recently provided strong additional evidence for the presumed role of this enzyme as one of the physiologic participants in the reactions involved in the metabolic pathway of neutral fat.

Since, on the other hand, evidence has been presented to show that old age is accompanied by a prolonged and augmented postalimentary chylomicronemia (3, 21, 28) and hyperlipemia (13), suggesting some difficulty in the handling of absorbed fat, a study was undertaken to determine the possible influence of age on the clearing factor-response on administration of a constant small dose of heparin.

MATERIAL AND METHODS

Two groups of apparently healthy persons were studied. The young group consisted of 27 members of hospital personnel, 20 to 39 years of age (mean age 28). The old group included 28 persons aged from 63 to 92 years (mean age 76) hospitalized at the Municipal Home of Helsinki primarily for social reasons. The members of the latter group were as normal as is possible among individuals of this age, and in any case had no manifest infectious, malignant, metabolic or coronary heart disease (erythrocyte sedimentation rate was normal).

All experiments were carried out in the morning on fasting subjects. After a control blood sample was taken, 15 mg. of heparin (Vitrum) was injected intravenously and exactly 30 minutes later a second specimen of blood was drawn. The blood samples were stored at 4 C., and the serum was separated from both specimens within 6 hours. Immediately thereafter the samples were assayed for clearing activity by the following technique.

A mixture of 0.6 ml. of the serum to be tested, plus 0.4 ml. of Tween-stabilized 0.25 per cent emulsion of pure triolein plus 2.0 ml. of physiologic saline were incubated at 37 C. and the decrease of optical density during 30 minutes was recorded with a Beckman B spectrophotometer at 620 millimicrons, using a 10 mm. light path. If any change occurred in the preheparin sample, the increase or decrease in the optical density was added to or subtracted from the clearing in the post-heparin sample.

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It was ascertained that storage of the blood at 4 C. for 24 hours did not change the lipemia clearing activity measurably; repeated measurements of the same serum samples on different days gave clearing values not deviating from each other more than 0.010 o.d. In 5 subjects the heparin injection and clearing measurements were repeated on different days; the maximal difference observed between the duplicate experiments was 12 per cent.

RESULTS

The results are presented in figure 1. The mean clearing/30 minutes in the young group is 0.060 ± 0.007 and in the old group 0.023 ± 0.004. It thus seems that the ability to form (or release) the clearing factor on administration of a small dose of heparin is definitely impaired at high age. Although the values within the young group are widely scattered, the difference between the means is still highly significant ($P < 0.01$). No significant correlation was found between the clearing activity and the serum cholesterol level.

DISCUSSION

There is at present no definitely established reason to claim that the observed age difference in the ability to form (or release) the clearing factor on administration of heparin would offer an explanation for the prolonged postalimentary hyperlipemia and chylomicronemia reported to occur in old age. Conclusive evidence for the physiologic significance of the clearing factor in the fat metabolism of man is still lacking. Although Jeffries (17) has been able to demonstrate high clearing activities in rat plasma during the fat absorption period, similar experiments in man yield positive results only occasionally and even then the clearing is only one-tenth of that in the rat (25). This failure need not, however, absolutely exclude the clearing factor as a physiologic participant also in the removal of neutral fat from the human circulation. As suggested recently by Anfinsen (1) on the basis of the experiments of Korn (19) and as is the case with other serum enzymes, the main site of the physiologic action of this enzyme can well be in the various tissues (muscles, adipose tissue, etc.). From there it probably is continuously released in small amounts into the circulation, but because of the presence of inhibiting compounds it is not demonstrable in blood under basal conditions. During the postalimentary hyperlipemia it may be assumed that an increased release of the tissue enzyme occurs into the blood, thus resulting in definitely demonstrable clearing activity in the rat plasma, in which the amount of inhibitory lipoproteins is low, but not in the human plasma, which has a relatively high cholesterol content.

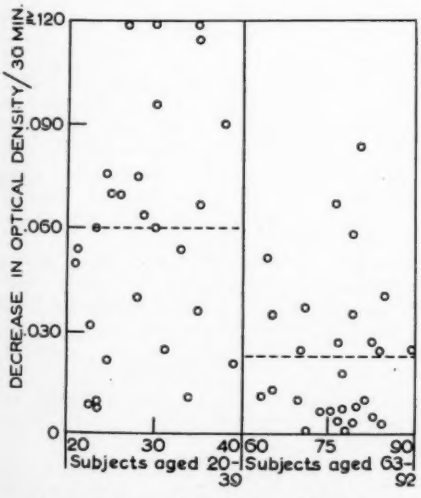

Fig. 1. Clearing of triolein emulsion by postheparin serum of normal persons of various ages.

Attempts to find a difference between presumably normal and atherosclerotic individuals in the clearing of alimentary lipemia by a constant dose of heparin have produced conflicting results. Thus, Block, Mann, and Barker (4) found a significant decrease of the in vivo clearing in atherosclerosis. On the other hand, in the few cases studied by Herzstein, Wang, and Adlersberg (14) no significant difference in the clearance of neutral fat after heparin injection was revealed between normal and atherosclerotic individuals. Similarly, Hood and associates (16) have presented evidence for an unimpaired formation of the clearing factor and a normal clearing process in atherosclerosis. According to Block and associates (4) as well as Grüner and associates (11), age has no influence on the clearing of lipemic plasma by heparin in vivo. Due to the continuation of the clearing in postheparin blood samples in vitro, the results of the in vivo clearing experiments are but of little value unless care is taken to inactivate the factor immediately after the blood is drawn.

In a series such as the present, it is impossible and meaningless to differentiate between the effects of atherosclerosis and of mere age. In view of their high age, the members of the old group presumably were not individuals with strong atherogenetic activity. This atherogenetic factor has worked in them a much longer time than in the younger group and thus led to more extensive atheromatous lesions of the arteries. If any increase in the rate of development of atherosclerosis occurs with increasing age, its cause must be some metabolic change produced by aging itself. The relative difficulty of taking up the absorbed fat from the circulation and the decreased clearing factor response to heparin may well be reflections of this change. On the whole the problem is linked to the basic biochemistry of aging, the knowledge of which is still very fragmentary.

The present investigation does not permit any conclusions on the cause of the observed difference. If heparin is assumed to be only an activator or liberator of a tissue lipase, the poor clearing activity is either caused by a deficiency of the latter or by an increase of inhibitors in the plasma. Cholesterol is known to be an inhibitor of the clearing factor, but neither in the present series nor in another study on this subject (26) has any distinct correlation been found between the inhibition of clearing activity and the serum cholesterol content. A study on the relation of clearing factor response to body fatness is in progress.

SUMMARY

To determine the possible influence of age on the ability to form (or release) the clearing factor, 15 mg. of heparin was administered to 27 persons aged 20 to 39 years and to 28 persons aged 63 to 92 years. The clearing activity of serum drawn 30 minutes later was assayed in vitro. The measurements revealed an average clearing of the serum equivalent to a decrease in optical density of 0.060/30 min. in the young group, and of 0.023/30 min. in the old group.

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ON PENICILLIN LEVELS IN YOUNG AND GERIATRIC SUBJECTS

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Numerous factors affect the penicillin levels in the organism. In addition to the type and amount of the penicillin used, the functional capacity of the kidneys is known to be of great importance; in renal insufficiency penicillin remains in the blood considerably longer (9). The shape of the penicillin concentration curve also seems to change according to whether the patient is in movement or at rest during the period of resorption of the injected drug, the curve becoming steeper with movement (5, 11, 12). On the other hand, penicillin blood levels have been found to rise with age although no renal insufficiency could be diagnosed clinically (2, 14, 17). This same phenomenon was very clearly manifested in our preliminary work (1) the results obtained with a series of 18 patients are included in the material of the present study.

As the destruction and inactivation of penicillin in the organism were found to be of no practical importance (10), concentrations of injected penicillin are affected only by the following 3 simultaneously acting factors: the rate of resorption, the diffusion of the penicillin in the tissue fluid and tissues, and its excretion which, again, takes place predominantly through the kidneys. The purpose of the present investigation has been to study the differences caused by age in the G-penicillin and procaine penicillin levels of geriatric and young test subjects both in the serum and in cantharidin-induced blister fluid. Cantharidin-induced blister fluid is the tissue fluid accumulation most easily available (although admittedly inflammatory), and as far as we can see the quality of blister fluid does not differ in any important respect from the normal tissue fluid, especially since the blister, when the specimen is drawn, is already mature and its fluid amount is at its maximum.

The experiments were carried out on 42 young subjects, 23 men and 19 women (15-33 years, mean age 24.8 years) and on 37 geriatric subjects, 5 men and 32 women (71-86 years, mean age 76.7). All the individuals were hospitalized and remained in bed for the period of the investigation; the subjects did not follow any special dietary regimen during the experiments. None of the patients of the geriatric

TABLE 1. G-PENICILLIN, SERUM LEVELS.

No.	Body Weight (Kg.)	½ Hour	1½ Hours	3 Hours	6 Hours
Geriatric Patients					
1	57.6	3.50	1.50	0.35	0.02
2	47.8	4.50	4.00	1.30	0.08
3	67.0	11.20	7.20	1.05	0.22
6	....	5.10	4.20	1.70	0.19
9	....	4.50	6.10	0.50	0.15
10	....	1.80	1.00	0.80	0.08
11	....	5.25	4.20	1.65	0.70
12	76.0	4.60	3.70	1.15	0.28
13	....	8.00	1.05	1.00	0.15
17	59.2	1.00	0.80	0.35	0.05
18	52.5	....	5.60	0.80	0.00
19	59.4	4.40	2.10	0.76	0.10
24	....	3.00	2.20	0.05	0.01
25	45.9	....	10.00	1.80	0.20
29	47.4	1.00	3.30	0.70	0.10
30	60.0	3.00	3.00	1.30	0.10
31	....	....	3.70	0.90	0.00
32	38.3	3.60	1.40	0.38	0.10
36	61.0	4.00	2.80	0.78	0.10
Means	57.2	4.32±0.52	3.57±0.51	0.97±0.11	0.14±0.028
Young Patients					
42	56.4	1.35	0.80	0.05	0.00
43	62.0	4.00	1.30	0.00	±
44	53.5	....	5.60	0.02	±
50	60.0	0.80	0.05	0.05	0.00
52	72.3	2.70	0.30	0.00	0.00
53	54.0	2.50	0.80	0.05	0.00
54	59.0	....	0.42	0.05	0.00
58	61.5	2.60	0.62	0.22	0.00
59	70.0	....	1.80	0.35	0.00
62	84.0	5.70	4.40	0.10	0.00
63	54.5	....	1.00	0.03	0.00
65	87.0	....	0.50	....	0.02
69	82.0	4.20	0.13	0.12	±
70	55.0	3.70	1.30	0.15	±
71	67.5	8.00	0.86	0.01	0.00
72	74.0	0.50	0.01	0.00	0.04
75	61.0	0.90	0.30	±	0.00
76	53.8	4.00	0.40	0.00	0.00
80	80.0	3.30	0.45	0.07	±
Means	65.7	3.16±0.52	1.11±0.27	0.07±0.018	0.003±0.0017

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TABLE 2. G-PENICILLIN, BLISTER LEVELS.

No.	Body Weight (Kg.)	1½ Hours	3 Hours	6 Hours
Geriatric Patients				
7	57.6	0.20	....	....
9	....	....	0.40	0.40
10	72.0	....	0.58	0.025
13	....	....	6.00	0.15
15	80.6	0.20	....	....
16	43.5	3.20	2.00	0.35
17	59.2	....	0.90	0.00
18	55.6	4.30	0.60	0.10
20	52.5	2.00	0.20	±
24	....	....	0.30	0.00
25	45.9	1.80	1.00	0.70
26	63.5	3.00	....	0.30
27	75.9	1.50	1.50	2.00
28	73.0	5.00	1.10	0.10
32	38.3	....	0.62	0.04
33	60.2	1.00	....	0.20
34	....	....	....	0.10
35	95.6	2.00	....	1.00
36	61.0	....	0.80	0.10
37	57.0	2.00	0.35	0.05
Means	62.0	2.18±0.41	1.17±0.29	0.31±0.096
Young Patients				
39	48.6	0.20	0.30	0.10
40	53.0	0.90	0.10	0.01
42	56.4	....	0.15	0.01
44	53.5	0.75	0.56	0.07
45	58.0	0.40	0.04	0.00
48	47.7	3.00	0.25	0.01
49	67.5	0.25	0.20	0.05
50	60.0	....	1.80	±
53	54.0	....	0.28	0.02
54	59.0	1.10	0.61	0.00
59	70.0	2.00	0.35	0.05
63	54.5	1.25	0.18	0.00
64	57.6	0.50	0.10	0.01
68	54.8	2.00	0.20	0.10
77	55.5	0.60	0.60	0.15
79	54.1	....	0.10	....
Means	56.5	1.08±0.25	0.36±0.083	0.04±0.013

group showed albuminuria, whereas albuminuria was present in 2 of the young subjects (no. 40 and 68). The blood non-protein nitrogen level was normal in all the individuals studied. The body weight was recorded in all instances in which weight measurement was possible; the observed values have been included in the tables. The body weight was not taken into account in determining the dose of penicillin to be administered. A total of 371 penicillin level determinations were made in the study.

In the experiments with the G-penicillin the patients were given 200,000 units of Leopenicillin (Medical Suppliers, Leo) dissolved in 2 ml. of physiologic saline solution, the injection being made deep into the gluteal region. The blood samples were taken ½, 1½, 3, and 6 hours after the injections, and centrifuged. To produce the skin blisters, three discs of cantharidin mixture (Cantharis 25.0, Oleum sesami 13.0, Cera flava 50.0, Terebinthina 12.0) (6), 1 mm. thick and 12 mm. in circumference, were attached to the patient's abdominal skin with adhesive tape 12 hours before the penicillin injection. Samples were drawn from these blisters 1½, 3, and 6 hours after the administration of penicillin (one-half hour after the injection the blister fluids contained so little penicillin that its quantitive determination could not be accurately carried out). Penicillin levels were determined by a modified (4) WHO Sarcina lutea Cup-Plate method (16).* The results ob-

TABLE 3. PROCAINE PENICILLIN, SERUM LEVELS.

No.	Body Weight (Kg.)	12 Hours	36 Hours	60 Hours
Geriatric Patients				
4	46.7	0.25	0.08	0.03
5	....	0.58	0.30	0.23
8	43.5	0.70	0.34	0.10
14	59.5	0.66	0.30	0.15
21	55.5	0.28	0.12	0.042
22	....	0.60	0.40	0.042
28	73.0	0.20	0.10	0.05
33	60.2	0.40	0.10	0.02
36	61.0	0.38	0.27	0.10
38	....	0.50	0.20	0.15
Means	57.0	0.46±0.062	0.22±0.041	0.09±0.022
Young Patients				
41	54.6	0.50	0.30	±
46	53.9	0.19	0.15	0.12
47	58.6	0.20	±	0.00
55	51.7	0.30	0.30	0.05
56	71.0	0.20	0.00	0.00
57	64.0	0.20	0.00	0.00
60	75.0	0.30	0.043	0.034
61	....	0.58	0.15	±
66	65.0	0.38	0.00	0.00
67	63.5	0.54	0.12	0.00
73	70.3	0.25	0.16	±
74	....	0.34	0.15	0.032
78	54.2	0.34	±	0.00
81	44.0	0.52	0.36	0.08
Means	60.4	0.35±0.038	0.12±0.034	0.023±0.001

* The determinations were made by Mrs. Helvi Vilppula, M.Sc., and Mrs. Merimaija Kyti, M.Sc., of the Microbiological Laboratory of Medical Suppliers Orion, Helsinki.

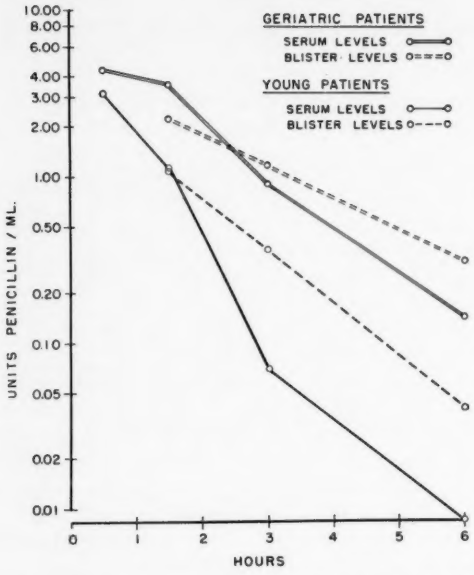

Fig. 1. Mean serum and cantharidin blister levels in geriatric and young patients after intramuscular injection of 200,000 units of G-penicillin.

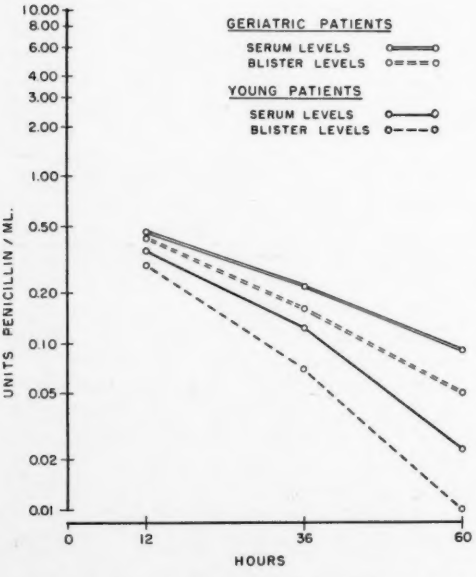

Fig. 2. Mean serum and cantharidin blister levels in geriatric and young patients after intramuscular injection of 600,000 units of procaine penicillin.

tained with G-penicillin are shown in tables 1 and 2 and the mean values in figure 1. Attempts to determine the penicillin secreted into the urine had to be abandoned because of the practical difficulties (catheterizations, urinary incontinence, etc.) encountered with the geriatric patients.

Six hundred thousand units of procaine penicillin (Procapen, Medical Suppliers Orion, Helsinki) were injected into the gluteal muscle and specimens were drawn 12, 36, and 60 hours after the injection. A disc of cantharidin mixture was applied to the skin 12 hours before each sample was drawn. The results are shown in tables 3 and 4 and in figure 2.

The maximum serum level of penicillin is usually found 15-30 minutes after an intramuscular injection (9). The half-hour values seem to indicate that no appreciable differences exist in penicillin resorption between the two age groups studied and that the initial resorption of penicillin is so rapid that the other factors have less chance of affecting the shape of

TABLE 4. PROCAINE PENICILLIN, BLISTER LEVELS.

No.	Body Weight (Kg.)	12 Hours	36 Hours	60 Hours
Geriatric Patients				
4	46.7	0.80	0.20	±
5	....	0.02	....	....
14	59.5	0.34	0.08	0.075
21	55.5	0.25	0.032	0.00
22	....	0.40	0.29	0.048
28	73.0	0.20	0.10	0.05
33	60.2	1.50	0.20	±
36	61.0	0.24	0.24	0.13
38	....	0.05	0.10	0.10
Means	59.3	0.42±0.14	0.16±0.039	0.05±0.018
Young Patients				
41	54.6	0.50	0.10	0.00
47	58.6	....	±	0.00
55	51.7	0.20	±	±
56	71.0	0.28	0.00	0.00
57	64.0	0.20	0.02	0.00
60	75.0	0.17	0.10	±
61	....	0.45	0.10	0.03
66	65.0	0.24	0.21	0.032
67	63.5	0.40	0.00	0.043
73	70.3	....	....	±
74	....	0.34	0.20	0.024
78	54.2	0.34	0.055	0.00
81	44.0	0.07	±	....
Means	61.1	0.29±0.041	0.07±0.024	0.01±0.006

the curve showing the penicillin level of the serum. On the other hand, later values reveal a clear difference between the age groups: after 1½ hours, the serum titer of the geriatric patients was 3.2-fold, and after 3 hours 12.9-fold that observed in the young subjects; after 6 hours very small amounts of penicillin were found in the serum in only a few individuals of the young group, while the corresponding mean concentrations of the geriatric patients were still therapeutically effective.

Factors accounting for this phenomenon might be that in geriatric patients the diffusion of the penicillin from the blood into the tissue fluid and the tissues is slower than in young patients, or that the amounts of fluid in the organism, because of possible dehydration, are smaller in the geriatric patients, as a result of which the penicillin level in the blood remains higher. However, dehydration is by no means enough to account for differences of such proportions. On the other hand, tissue fluid and intracellular fluid represent such a large quantity (tissue fluid approximately 15 per cent, intracellular fluid approximately 50 per cent) of body weight (6) that any difference in diffusion may affect the penicillin blood levels. The penicillin content of the lymph has been studied in dogs and it was found that the penicillin level of the lymph obtained from the thoracic duct after an intramuscular injection was approximately equal to the serum levels, but the peak occurred a couple of hours later (13). The results obtained from cantharidin blisters are on the same lines. No significant difference between geriatric and young patients was found in the interrelationship of the penicillin levels in the serum and the blister fluid. Thus, differences in diffusion (in any case from the blood to the tissue fluid) were not found to account for the higher serum penicillin levels of geriatric patients. It is interesting that the penicillin concentration of a mature blister varies so considerably in 1½ hours—evidence that the circulation of fluid is surprisingly rapid even in such a superficial blister.

The experiments made with procaine penicillin gave parallel results, except that the blister fluid levels remained constantly below the serum levels. It is remarkable that the geriatric patient resting in bed shows 0.09 units/ml. of penicillin in the serum, a fully therapeutic concentration, 60 hours after a penicillin dose of 600,000 units.

The higher penicillin levels of geriatric patients are obviously due to a poorer secretion of penicillin through the kidneys, as has been suggested before (2, 14). Approximately 80 per cent of the penicillin is known to be removed by active tubular secretion (2). The phenomenon studied, therefore, is probably associated with the general decrease in tubular secretion of the aged (3, 7, 15). The differences in concentration between the age groups may well be large enough to be of significance in the dosage of penicillin.

SUMMARY

A study was made of the serum and cantharidin blister fluid levels of G- and procaine penicillin administered intramuscularly in young and old test subjects. The levels in geriatric patients were found to be considerably higher. No differences between the age groups studied were observed in the resorption of penicillin from the site of the injection or in its diffusion from the blood into the tissue fluid. It is concluded that the responsible factor is decreased tubular secretion of the compound.

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A STUDY OF AGE DIFFERENCES IN THE X-RAY DENSITY OF THE ADULT HUMAN CALCANEUS—VARIATION AND SOURCES OF BIAS*

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During recent years several studies (4, 9, 10, 11, 12)‡ have been made of living human bone x-ray density, measured by photometer and expressed as thickness of an aluminum or ivory wedge exposed simultaneously on the same film, but little information regarding age differences has appeared. The search for such information requires strict attention to subject-selection methods, to variation arising from techniques (x-raying, processing, and densitometry), and to differences between subjects of the same age. Cadavar bone experiments (16) have shown that, even with an inexpensive densitometer, variation due to technique can be reduced to a satisfactorily low level; and the present report carries the study to a tarsal bone easily investigated during life, the calcaneus. This investigation analyzes the variation into its components (reading error, variation between repeat films, subjects and sides, right and left), and thus a search for age differences has provided information necessary in attempts to form standards of "normality" and to estimate density changes in diseased persons.

Throughout the report the term "bone density" is used to mean "bone shadow density," or "opacity to x-rays." Because of the masking effect of overlying soft tissue and of the organic constituents of bone, the exact relationship of bone shadow density to mineral density is unknown. For the present, photometry of bone shadows should be regarded simply as a substitute for visual assessment. It is more objective and more precise than the eye, and it permits correction for interfilm and intersubject differences in the thickness and opacity of overlying soft tissue. As pointed out elsewhere (16), its crudity as a measure of tissue phenomena (mineral changes) is shared by many biochemical and physiologic tests which are, nevertheless, used for clinical and research purposes.

METHODS

Subjects.—The male subjects were 50 white men, aged 20 to 84—students, technicians, university teachers, other professional and business men, almost all of British origin, living in or near Halifax, Canada, in 1947 or 1949. Twelve women, similarly characterized but aged 19 to 30, were also x-rayed. Clinical histories were taken, but a full clinical examination could not be imposed on busy persons who came voluntarily to the Dalhousie University Anatomy Department twice for x-raying and again for physiologic tests (18). The term "healthy," therefore, implies symptom-free, without history of bone or joint disease or of injury to the region x-rayed (except for bruises, ankle sprains, and one Pott's fracture 44 years previously). The films themselves showed no signs of disease or injury.

Roentgenography.—A rotating-anode tube with 1.2 mm. focal spot, at 6 feet above the table to minimize distortion, was centered at the middle of the ankle (tibio-talar) joint to give a medio-lateral film. Exposure: 100 ma., 0.4 sec., 71—76 kv.p. according to thickness of the part.

Eastman Kodak no-screen films, 10 × 12 in. and 11 × 14 in., were enclosed, for table-top exposure to avoid grid lines, in negative preservers, along with light-proof paper, a masonite board ⅛ in. thick, and a lead sheet. Exposed posterior to the leg and foot was an aluminum wedge (Alcan alloy 17ST) with 25 1 mm. steps, precision-milled and measured. An antero-posterior ankle film was also made.

One person (D.M.) did all the positioning, another (R.B.M.) made all the exposures and did all processing. All the women and 8 men were x-rayed in 1947, the rest in 1949.

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‡ A fuller bibliography is given in a detailed report on technique experiments.

Visits and Sides (Right and Left).—Except for 3 men who, for reasons unconnected with age or bone density, were x-rayed only once, all subjects paid a second visit, the interval being usually 2—4 weeks (in one man, 3 days; in 3 men, 5 weeks). Because many films of other parts were taken, it was undesirable to film both feet on the same visit. All possible $Visit_1$ - $Visit_2$ sequences (RR, LL, RL, LR) were used, but in unequal numbers, because they were part of another investigation to be described later.

The sequences were allocated to the subjects by random numbers, but it was impossible to randomize subjects (i.e., ages) throughout the x-raying period. However, bias due to a trend, or nonrandom fluctuations, in x-ray equipment or processing seems unlikely because (a) the sequence of ages was very irregular, with young and old men often adjacent, (b) correction of bone density by soft tissue density, affected identically by differences in x-raying and processing, would tend to remove the bias, and (c) the lapse of two years between two groups, mentioned above, apparently produced no systematic difference in density estimates.

Densitometry.—Equipment: Photovolt transmission densitometer—Model 52 transmission density unit (light box) with 1/16 in. aperture; Model 501A spot photometer. Each film was in an envelope composed of two 0.01 in. cellulose acetate sheets, a new envelope being started after every fiftieth film. Tracing paper was clipped to the envelope and, on a horizontal viewing box, pencil marks were made (fig. 1):

1. A line from the postero-superior angle of the calcaneus to the antero-inferior angle, divided into 10 equal parts (9 points).

2. A point on the plantar soft tissue 0.5 cm. below the bone at the midpoint between the antero-inferior end of the tuber calcanei and the anterior tubercle of the bone.

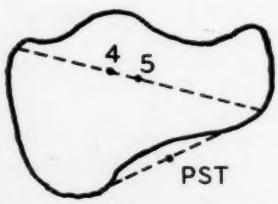

Fig. 1. Left calcaneus on medio-lateral film, to show where densities were read. 4 and 5 = 4th and 5th of 9 equally spaced points on the tracing line. PST = plantar soft tissue.

3. The centers of the first 10 steps of the aluminum wedge.

Each of the marked points was centered over the densitometer aperture, the tracing paper was turned aside, and a reading was made on the light-unit scale. All films were read by one person (H.H.W.) in 1954, in strictly random order, with operating rules (16) that insured stability (tested by a standard film) throughout the 6 weeks occupied by 2 complete rounds of readings.

Bone and soft tissue readings were converted into millimeters of aluminum by linear interpolation between the steps. Because the first and ninth points on the calcaneus line varied greatly between repeat films (due doubtless to slight differences of orientation of the foot), while the remaining points were very much alike on any one bone, the mean aluminum thickness for only the central region (fourth and fifth points) was used in the analysis.

Concomitant Variates.—On each visit stature was measured, without shoes, by a steel scale fastened to a wall; weight by a beam scale, with adjustment for clothing. To obtain a simple measure of bone width in the region x-rayed, on the antero-posterior films the transverse ankle-joint axis was measured to the nearest millimeter by a transparent scale along the inferior margin of the tibia—two rounds of readings by the same person (H.H.W.).

Correction for Differences in Bone Width and Soft Tissue.—The common method of allowing for bone width (thickness) and for overlying soft tissue is by information from a film at right angles to the bone density film. From soft tissue readings (thickness and density) on the supplementary film, an amount can be calculated to subtract from the bone density in order to obtain a net value, expressible as millimeters of aluminum per centimeter of bone thickness. This seems to be, in essence, the method applied by Mack and her collaborators (3, 9, 10, 11) to the calcaneus. An undistorted supero-inferior calcaneus roentgenogram is, however, difficult to obtain, especially in subjects whose ankles are not very flexible, and the present investigation used a regression (covariance) method instead.

The plantar soft tissue (PST in fig. 1) comprises (a) tissue continued down from the sides of the calcaneus, and (b) tissue below the bone and corresponding to it in width. Hence, in any series of films the correlation between

plantar soft tissue density and bone density will to a large extent reflect the contributions of overlying soft tissue density and thickness, and of bone width, to the intersubject bone density differences. The scatter of points (individual subjects) around the regression line (bone density on soft tissue density) will represent mainly the variation in bone density due to other factors than soft tissue and bone width, especially intersubject differences in true (net) bone density. (In this series there was no suggestion of a curvilinear regression, but that does not imply that one could safely extrapolate linearly to zero density for soft tissue to find the average net bone density.)

Statistical Analysis.—Methods familiar to biologists were used throughout (5, 6, 13, 20). When a P value is not specified, the 5 per cent level is implied as the standard.

RESULTS

Differences between Densitometer Readings

The first round of readings did not produce significantly higher (or lower) bone density estimates than those of the second round. Therefore the data from 128 films were pooled to give an estimate of random (variable) error —standard deviation (SD) of the difference between two estimates from the same film = 0.195 mm. aluminum. Since the frequency distribution was roughly normal (Gaussian), in about 95 per cent of duplicate readings the estimates of bone density could be expected to differ by less than $2 \times 0.195 = 0.39$ mm. This is 5.3 per cent of the mean density (7.4 mm.) of all the bones used—a reasonably high precision; but the important question is: How much does reading variation contribute to intervisit and intersubject differences? Estimates of this will be shown below.

Differences between Right and Left Calcanei

In men who had different sides, right and left, x-rayed on the two visits, there was no significant difference between visits or between sequences (RL versus LR); therefore 31 such men were treated as one series. In 8, the L-R difference was negative, in 23 positive—a significant majority (13); P less than 0.05. The mean of the 31 differences (L-R) was +0.270 mm. aluminum (t = 2.87; P less than 0.01).

The differences ranged from −1.22 to +1.59; and the SD of the series was 0.431. This was larger (P less than 0.02) than the SD of differences, given below, for duplicate films of the same bone, 0.234 mm., which represented technique effects. The most plausible explanation is that men actually differed in the L-R density difference, and that some had negative differences.

The L-R difference could not be explained by differences in soft tissue density or in adjacent bone width (ankle axis). Differences in wedge position can create differences in tissue density estimates (16), but this was an unlikely explanation because right and left soft tissue density did not differ significantly.

Further elucidation would probably require cadaver bones; but the finding has three features of some importance in the present study: (a) Precision of method. The mean difference (+0.270 mm.) was only 3.54 per cent of the general mean density of this series (7.63 mm.), (b) Value of *intrasubject* comparison (contrast the nonsignificant R-L difference found in the comparison of RR and LL subjects, below), (c) Importance of adhering to one side (R or L) if both sides are not to be examined.

Differences between Visits of the Same Person

Intersubject Variation of Differences.—In 16 men the same calcaneus was filmed on both visits (RR in 8, LL in 8), and the mean of the 16 differences, $Visit_1 - Visit_2$ did not differ signiflcantly from zero. Coefficient of correlation between bone density difference and soft tissue density difference = +0.85. Therefore 0.85^2 (= 72 per cent) of the intersubject variation in the intervisit difference in bone density was represented by linear regression of $V_1 - V_2$ for bone on the corresponding difference for soft tissue.

The residual intersubject variation was represented by a standard deviation of 0.234 mm. aluminum, and this is the quantity that, if derived from a larger sample (say 100 or more), would be used in determining whether, in the interval between two visits, a person's bone density had changed more than the difference in soft tissue density would lead one to expect. Beyond the expected value of $V_1 - V_2$ for bone density, obtained from the regression equation, an allowance would be made for intersubject variation in $V_1 - V_2$ before concluding that a real change in bone density had probably occurred. If the standard deviation were the same as in the 16 men, an allowance of ± 2 SD would be ± 0.468 mm., which, incidentally, is 6.2 per cent of the mean density (7.61 mm.) in this sample.

Contribution from Reading Variation.—The standard deviation 0.234 mm. was obtained by using the mean of two rounds of readings per film. Analysis of components of variance (20) showed that if there were only one reading round the SD would be 0.29 mm.; if three rounds, 0.21 mm.; if no reading variation (or if the average of very many rounds were used), 0.15 mm. Two reading rounds are desirable, not only to increase precision, but to allow detection of gross slips. A larger number, within practical limits, is hardly worth the effort.

Differences between Subjects

Components of Intersubject Variation.—The 16 men whose second visit entailed a re-examination of the same calcaneus showed a hardly discernible, and far from significant, difference between right and left mean bone densities (LL — RR = +0.005 mm.). Therefore all 16 men were grouped (both reading rounds from both films) to give a general mean density = 7.61 mm. After correction for soft tissue (intersubject r = +0.72) the intersubject SD for bone density was 0.417 mm. Analysis of components of variance gave the following estimated SD's in mm. aluminum.

1 visit (i.e., 1 film), 1 round: 0.451;
1 visit, 2 rounds: 0.432;
2 visits, 1 round each: 0.445;
2 visits, 2 rounds each (the actual case): 0.417;
If no intervisit or inter-reading variations: 0.401.

To reduce the variation, two readings for one visit (one film) seem, if anything, to be more effective than two visits with only one reading for each. If confirmed, this could save much time, labor, and expense. The main component was, however, contributed by actual intersubject differences, which might, of course, contain some technique variation greater than occurred between visits of the same subject.

Correction of Intersubject Bone Density Variation by Soft Tissue.—In the 42 men whose left calcanei were filmed (one film each, two reading rounds per film), r for soft tissue and bone density was +0.708. Therefore correction for soft tissue removed approximately 50 per cent of the intersubject variation in bone density. With B = bone density, and ST = soft tissue density, both in mm. aluminum, the regression equation was:

$$B = 1.037ST + 1.691.$$

In the range of values observed (6.30—10.04 mm. for bone, 4.45—7.21 mm. for soft tissue) there was no suggestion of curved regression. The regression coefficient, +1.037, shows that, on the average, the bone density increased with soft tissue density approximately millimeter per millimeter.

The scatter of subjects around the regression line (residual variation) was represented by SD = 0.550 mm. aluminum, which was 7.1 per cent of the mean (7.741 mm.). This coefficient of variation is similar to that for the adult skull capacities (19), and lies between the coefficients for stature (3-4 per cent) and weight (10-14 per cent) in homogeneous populations (7, 19).

Although x-ray technique was very uniform, subsequent experiments (16) have shown that variation could be reduced still further by additional precautions (e.g., uniform kilovoltage, position of film in developer, duration of washing); but it should be mentioned that in this calcaneus series no effect of the 6 kv.p. range was discernible.

Concomitant Variates

For three of the concomitant variates studied in the series of 42 men whose left calcaneus densities were studied, some basic data should be mentioned here (mean, intersubject SD, coefficient of variation, CV).

Stature: Mean = 68.50 in. SD = 2.54 in. CV = 3.7 per cent.
Body weight: Mean = 153.26 pounds. SD = 22.55 pounds. CV = 14.7 per cent.
Ankle axis: Mean = 3.47 cm. SD = 0.21 cm. CV = 6.0 per cent.

The figures for stature and weight show that the sample was not at all peculiar in these features. No data for comparison with ankle axis figures were known.

Zero Order Correlations.—From the 42 men the following 15 correlation coefficients were obtained:

Correlation of *bone density* and:
Soft tissue density, +0.708 (P very small)
Ankle axis, +0.384 (P = 0.02—0.01)
Stature, +0.193 (P = 0.3—0.2)
Body weight, +0.465 (P = 0.01—0.001)
Age, –0.035 (P = 0.9—0.8)

Correlation of *soft tissue density* and:
Ankle axis, +0.252 (P = 0.2—0.1)
Stature, +0.185 (P = 0.3—0.2)
Body weight, +0.435 (P = 0.01—0.001)
Age, – 0.268 (P = 0.1—0.05)

Correlation of *ankle axis* and:
Stature, +0.512 (P less than 0.001)
Body Weight, +0.218 (P = 0.2—0.1)
Age, –0.215 (P = 0.2—0.1)

Correlation of *stature* and:

Body weight, +0.347 (P = 0.05—0.02)

Age, –0.452 (P = 0.01—0.001)

Correlation of *body weight* and:

Age, –0.220 (P = 0.2—0.1)

Elimination of Variates.—In order to interpret some of the foregoing relationships and to see which of them could be disregarded in establishing standards for the assessment of bone density, coefficients of partial correlation were found. The chief results (with zero order coefficients repeated in parentheses) are as follows:

1. Bone density and soft tissue density (+0.708). Elimination of ankle axis, body weight, or stature: trivial changes.

2. Bone density and body weight (+0.465). Elimination of ankle axis: slight change. Elimination of soft tissue density: reduction of r to +0.247 (P = 0.2—0.1). Correction for body weight, therefore, seems unnecessary.

3. Bone density and ankle axis (+0.384). Elimination of stature or weight: slight change. Elimination of soft tissue density: reduction of r to +0.302 (P = 0.1—0.05). The soft tissue correction, therefore, compensated for bone width, so far as measured by ankle axis; and this, if clearly confirmed, could obviate the need for an antero-posterior film.

Relationship of Bone Density to Age

Age Distribution.—The attempt to obtain equal numbers of men in each decade was not very successful, as is shown by the frequency distribution of ages (to the nearest year) for the 42 men who provided films of left calcanei.

Age	*No.*	*Age*	*No.*
20-24	8	55-59	3
25-29	3	60-64	2
30-34	3	65-69	3
35-39	4	70-74	5
40-44	5	75-79	—
45-49	2	80-84	1
50-54	3	Total	42

Correlation of Bone Density and Age.—For bone density and age, r was small (–0.035) and far from significant. For soft tissue and age, it was –0.268, which may be fortuitous (P= 0.1—0.05) or may reflect a negative correlation between age and body size, manifested also by stature, weight, and ankle axis. (There was no reliable measure of actual soft tissue thickness.)

After soft tissue correction, r for bone density and age was +0.227 — still not significant (P = 0.2—0.1). Correction for body weight as well as soft tissue increased the value slightly, to +0.266 (P = 0.1—0.05).

A correlation coefficient reflects an average straight-line relationship. Therefore a curve, rising early and horizontal or descending later, could produce a nonsignificant correlation coefficient; but a dot diagram gave no suggestion of this. The equation for bone density in mm. aluminum (B), age in years (A) and soft tissue density in mm. aluminum (ST) was:

$$B = 0.007A + 1.103ST + 0.993$$

Possible Values of Coefficients.—Even if the relationship found here (r = +0.227 and a regression coefficient, b = +0.007, indicating an average yearly increase of 0.007 mm. aluminum) were due to more than chance, little benefit would accrue from an age correction in assessing an individual's bone density. However, the true (population) values may differ from those estimates. The 95 per cent confidence limits found by normal-curve methods were presumed fairly safe in view of the fact that, after correction for soft tissue, the residual bone density variation showed over-all agreement with the normal (Gaussian) distribution, for g_1 and g_2 (Fisher, 5) were far from significant (P greater than 0.7).

The limits for r, obtained from Fisher's z transformation were –0.09 and +0.50. The limits for b, from twice its standard deviation, were –0.003 and +0.017.

Comparison of Women with Men

The 12 women, aged 19 to 30, were investigated only to see if they revealed any marked difference from men. Since no R – L distinction was detected, the values from all women (means of both visits) were used in most analyses; but even with 12 subjects, r must be 0.576 for significance at the 5 per cent level (6).

Correlation Coefficients.—Of the 15 correlation coefficients corresponding to those given above for men, two, marked by asterisks below, differed significantly from the male values, and only 5 of them were significant:

Bone and soft tissue densities, +0.77 (P = 0.01—0.001)

Bone density and body weight, +0.59 (P = 0.05—0.02)

Soft tissue density and body weight, +0.66 (P = 0.02)*

Ankle axis and stature, +0.66 (P = 0.02)

Stature and body weight, +0.62 (P = 0.05—0.02)*

Elimination of soft tissue density reduced the r for body weight and bone density to +0.18 (P = 0.7—0.6).

For bone density and age, r was –0.29 (P = 0.4—0.3), and this was not significantly changed by allowing for the correlation between age and soft tissue density (r = –0.11; P = 0.8—0.7).

Residual Intersubject Variation.—In the 10 women whose left calcaneus was x-rayed, after allowance for soft tissue, the intersubject SD was 0.368 mm. — not significantly different from the SD for men (0.550 mm.).

Comparison of Means.—The effectiveness of the soft tissue correction was seen in comparing the means for bone density in the 42 men and the 10 women. Before correction, the means (mm. aluminum) were:

Men.—Bone, 7.74. Soft tissue, 5.83
Women.—Bone, 6.60. Soft tissue, 5.00
Difference in bone density = 1.14 mm. (P very small).

After adjustment for the soft tissue difference by covariance (20), the bone difference was no longer significant (P = 0.2—0.1). If, for example, the mean soft tissue density for women had been the same as for men, the women's mean bone density would have been 7.44 mm., which is only 0.30 mm. less than the mean density in men—a nonsignificant difference. If this (and the nonsignificant sex difference in intersubject variation) were confirmed on larger samples through 5 or 6 decades, a table of norms could be common to both sexes.

DISCUSSION

Bias in Cross-sectional Surveys.—This study, like most other researches on aging in human adults, was necessarily a cross-sectional survey, which can tell us only about differences *associated with* age or the apparent lack of such differences. To equate such information to information about age *changes* would entail numerous risks of hidden bias. The risks are well known in general, but it is desirable to consider in each survey the specific mechanisms of bias relevant to it. In the present study 4 examples may be mentioned:

1. Young men and old men belong to different eras of hygiene and nutrition.

2. If differences in bone mineral content tend as life advances to be associated in any way with disease, younger men with a certain bone density will be accepted for the survey, but older men with the same density, if they have developed the disease (or are dead from it) will not be surveyed.

3. Even the restriction to professional and business men does not insure that the older men, when young, had the same habits (e.g., of food and exercise) as the young men. Medical students were easy to obtain, and so, to a fair degree, were full-time faculty members in the 30—65 age group, but medical practitioners and business men were not.

4. A bias that is less well known than the foregoing leads to what in this laboratory is called "Berkson's fallacy," after Dr. Joseph Berkson who first demonstrated it (1, 2). He showed how it can vitiate inferences regarding the causation of disease, but it can be equally serious in surveys of healthy persons (15). If a "selection rate" is defined as "the proportion of any group (e.g., an age group) that is included in a survey," the bias can be described as due to a "competition between selection rates," and the selection factors can be of any kind, including the psychologic factors (8) that cause persons to volunteer as subjects for an investigation.

To illustrate one mode of action of the bias, let it be supposed that there is no relationship whatever between age and bone density, but that differences in selection rates arise because (a) younger men are easier to obtain than older men; (b) men who are much concerned about health problems, including their own health, are more likely to volunteer than are other men; and (c) health-conscious men differ from the others, not only psychologically but somatically (e.g., biochemically) or in their habits of food and exercise. The first of these assumptions was validated in the present survey, and the other two are by no means unlikely.

If these assumptions are correct, and if any of the attributes in the third assumption are in any way associated with bone density differences, the densities commoner in health-conscious men will have the higher selection rates, and then the bias will enter. The mechanism has been demonstrated by simple arithmetical examples (14, 15, 17), but the effect can be described in general terms. If, for instance, the health-conscious men tended to have higher bone densities than other men, the higher selection rate of younger men would seem to push the higher densities into the older age groups, and there could arise a fallacious positive corre-

lation between bone density and age. Moreover, like any other bias, the selection-rate bias can hide a real (population) association between two attributes (or variates), or it can even produce, in the sample, an association in the opposite direction from the real association.

The biologic value of a human adult cross-sectional survey depends, therefore, on how far it can be supplemented (a) by animal studies (better-controlled cross-sectional surveys, longitudinal surveys and, in some instances, experiments), and (b) by short-term human longitudinal surveys. For the more immediate practical purpose of establishing norms for medical assessment, we must often rely solely on cross sections, and then we must remember that there may be great, and relevant, differences between volunteers for a survey and persons who are driven to a physician by illness or suspicion of illness.

In a study such as this it is important to compare the risks of bias in the two common types of standard required in clinical assessment: (a) normal intersubject variation in intervisit differences, and (b) normal intersubject variation in absolute measurements.

Variation in Intervisit Differences. — In healthy subjects intervisit differences, with intervals of only a few weeks between visits, presumably represent, not actual bone changes, but slight differences in positioning on the x-ray table, variation in x-ray factors (e.g., kilovoltage and the timing mechanism) and in the processing, because conversion of bone density to equivalent aluminum density does not entirely remove the effects of technique differences (16). Subject-selection factors, therefore, need cause little concern; but, of course, a much larger sample than the 16 men used in the present study would be necessary for definitive conclusions—not only to increase the precision of estimates, but to permit a search for curvilinearity of the bone-soft-tissue regression, for a non-Gaussian distribution of deviations from regression, for heterogeneity of this variance at different points on the regression line, and for a relationship between the intervisit difference and the absolute density .

To capture fully the fluctuations and drifts of technique, the standard series should be built up during the same period as films of subjects (e.g., patients) that are to be assessed retrospectively by the standard, and with the same interval between visits (e.g., 3 months). Since the standard series will be applied also to future subjects, its internal stability should be tested, and from time to time a new series of healthy subjects should be investigated.

The required sample size cannot, of course, be stated in advance, except with reference to the precision of estimates from samples whose parent populations are Gaussian, and then the information is obtainable by calculation from a table of variance ratios (6). For instance, if SD is a random-sample estimate from a normally distributed population with standard deviation = σ, the sample size should be at least 120 to permit the assertion with 95 per cent probability that σ does not exceed SD by more than 12 per cent of SD.

Variations in Absolute Measurements.—In order to establish a standard of intersubject variation in absolute bone density, our sample of 42 men would have to be enlarged for the same reasons as were enumerated regarding intervisit variation; but even the largest possible sample would not remove the risk of bias from selection-factors. In human norms all that we can attain is correction for sources of bias and variation discovered in a sample. For calcaneus density the present study strongly suggests that the only correction needed is for soft tissue density. This even compensated for differences in bone width in the ankle region as measured by the ankle axis, but it is still desirable to know whether some simple and reliable linear measurements, in addition to soft tissue correction, would not reduce the intersubject variation further than does the soft tissue correction alone. Age relationships, also, require further research, because they have biologic as well as medical interest.

Age Relationships.—The results did not even suggests the existence of an age difference in calcaneus density, and this may well be a true picture, because, as a rheumatologist reviewing this report pointed out, the calcaneus, perhaps owing to its weight-bearing function, seems to be a very stable bone, slow to show age changes, and not as readily subject to steroid deficiency osteoporosis as are many other bones.

If there were a real age difference in the bone density we should expect a negative correlation, because one of the features of senile osteoporosis is loss of mineral matter; but in this study the confidence limits for r (after correction for soft tissue) showed that if the correlation in the population were negative, its magnitude was

slight (probably not beyond –0.09), whereas if it were positive it might be almost +0.50.

If, however, we met a highly significant positive correlation, large or small, we should be strongly inclined to suspect that biased selection had produced it. Another possible explanation might be considered—that calcification in the arteries of some of the older subjects had been recorded as bone density. For arteries that are large enough to be visible, this risk can be avoided. For smaller arteries the soft-tissue correction could be expected to compensate to a large extent; but if the problem actually arose, the minimal size of a vessel subject to calcification would have to be considered, and perhaps it would be necessary to make a combined densitometric and histologic examination of amputated limbs containing calcified vessels.

The possibility of a positive value of r, shown by our upper confidence limit, is, therefore, probably to be regarded as a possibility of random sampling variation (which is all the confidence limit claims to be), and not as a biologic possibility. Nevertheless, further study of active symptom-free subjects in the later decades is desirable. In such a study a somewhat different x-ray technique might be tried, because kilovoltage, milliamperage, and exposure time in the present study were chosen to give details of soft tissue and of articular margins and were not perhaps ideal for the study of porosis in a bone covered by soft tissue.

The Establishment of a Standard Series.—A standard series of bone densities in healthy adults, with corrections for soft tissue and perhaps other variates, would be analogous to a table of body weights in which allowance is made for stature (and for age in children). For these simple measurements, however, large series can be obtained, at least in children, and limits such as the 10th and 90th percentiles, sufficiently precise for clinical assessment, can be determined by direct enumeration.

In bone density such large series cannot be expected because of (a) the complex and time-consuming procedure, (b) the scarcity of volunteers, and (c) the variation introduced by techniques, which makes it unwise, at present, to pool data from different laboratories. Consequently, allowance for concomitant variates must be made by regression.

First, it seems necessary that several independent studies should be made along the lines of the present one, but on larger samples, in order to establish (a) which of the possibly important variates (e.g., bone width and age) have statistically significant relationships with bone density, and (b) which of the variates shown to have a significant relationship, have an influence large enough to justify their use in correction terms—a more difficult question, to be discussed in a later report.

Secondly, with this information, methods of sampling and computation could be prescribed for other workers who wished to set up their own norms.

Finally, if techniques of x-raying, processing, and photometry became sufficiently standardized, more general norms, formed by pooling data from several centers, could be established.

SUMMARY

In medio-lateral roentgenograms of the calcaneus of 50 symptom-free Canadian white adult males (students, professional and business men aged 20 to 84) and 12 females of the same classes (aged 19 to 30), the bone shadow density, determined by Photovolt densitometer, was expressed as equivalent thickness of an adjacent aluminum step-wedge. Correction for interfilm and intersubject differences in overlying soft tissue density was derived from the linear regression of bone density on plantar soft tissue density. The following results seem noteworthy in attempts to establish norms:

1. From 128 films read twice independently by one person it was estimated that about 95 per cent of such duplicate values could be expected to differ by less than 0.39 mm. aluminum (i.e., 5.3 per cent of the general mean, 7.4 mm.).

2. For 16 men in whom the same calcaneus, right or left, was x-rayed on two visits usually 2-4 weeks apart (two readings per film), after soft tissue correction, the 2-standard-deviation allowance for intervisit variation was ± 6.2 per cent of the general mean; but for reliability of such an estimate more than a hundred men would be needed.

3. In the same 16 men the intersubject variation could be reduced as much by taking two readings from one visit (one film) as by requiring two visits and taking one reading from each.

4. In 31 men whose left and right calcanei were x-rayed, a mean left-right difference of +0.270 mm. aluminum was found (P less than 0.01)—an illustration of the precision of the method.

5. For the left calcanei of 42 men (one film read twice), the mean density = 7.741 mm. aluminum, intersubject standard deviation after correction for soft tissue = 0.550 mm., coefficient of variation = 7.1 per cent. This group provided the following information.

6. Bone density was not significantly correlated with stature, and its significant positive correlation with body weight was removed by adjustment for soft tissue density.

7. The significant positive correlation of bone density with the tranverse ankle axis, measured on an antero-posterior film, was reduced to a nonsignificant value by the soft tissue adjustment, which, therefore, compensated to a large extent for bone thickness in the region.

8. After soft tissue correction, there was no significant sex difference in mean density or in the intersubject variation of density.

9. After soft tissue adjustment, r for bone density and age in the 42 men was +0.227, a nonsignificant value (P = 0.2—0.1). The 95 per cent confidence limits for r were –0.09 and +0.50. Therefore, if these men could be taken as a random sample of their class, the conclusion would be that a negative correlation, if present, was trivial. The upper limit, being positive, probably represents only a random-sampling possibility, and not a biologic one. Because of the biologic and medical importance of age changes in bone density, however, the search should be continued, especially in the later decades.

Although numerous possible biases, discussed in this report, render cross-sectional surveys unreliable for discovering an age *change* or the absence thereof, such surveys cannot be avoided in attempts to establish clinical norms, and their results can often be elucidated by animal research and short-term human longitudinal studies.

Certain methods of establishing standard series are recommended.

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BOOK REVIEWS

BODY MEASUREMENTS AND HUMAN NUTRITION, edited by Joseph Brozek, Wayne University Press, Detroit, 1956, 170 pages, $3.50.

The book consists of the proceedings of the Conference on the Role of Body Measurements in the Evaluation of Human Nutrition, held at Harvard University in 1955, and sponsored by the Committee on Nutritional Anthropometry, Food and Nutrition Board, National Research Council.

The twelve papers exhibit several of the characteristics of modern biologic research. First, there is the concentration on the measurement of dynamic changes, an especially interesting development in "classical" anthropology. Second, the necessity for interdisciplinary efforts results in border-line disciplines. Here anthropology and nutrition join in an area described by Brozek as "nutritional anthropometry." The anthropologists are feeling their way in standardization of measurement techniques applied to rapidly changing soft tissues and body composition. The nutritionists are trying to utilize objective anthropometric measurements to quantitate nutritional changes. Both groups are studying the reliability and significance of these measurements.

From the gerontologic point of view, the work is of interest in that it offers the possibility of another technique which might be useful in future studies of the aging process.

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HORMONES AND THE AGING PROCESS, edited by Earl T. Engle and Gregory Pincus. Academic Press, Inc., New York, 1956. 323 pages, $8.50.

As a result of the relatively extensive advances made in the field of endocrinology during the past 3 or 4 decades, it is a logical sequence for this information to be correlated with the rapidly developing interest in gerontology. Attempting such a correlation, this book represents a transcription of the proceedings of the Conference in which 31 individuals participated for the purpose of bringing together basic endocrine findings with their clinical applications to the aging processes. Eighteen separate topics were included, each being prefaced by a pertinent introductory paper and followed by an active, informal, and stimulating discussion involving a number of participants.

The effects of advancing age on the qualitative as well as quantitative changes in the presence of various hormones and their derivatives were evaluated. The effects of these changes as well as the influence of the administration of certain endocrine preparations on nitrogen retention, muscle development, and general protein metabolism were discussed. The effects on the metabolism of sodium, potassium, calcium, and phosphorous were also included. In addition, such general subjects as the relationship of certain hormones to osteoporosis, malignancies, prostatic growth, cerebral metabolism, metabolic balances, and generally occurring pathologic conditions associated with aging were covered. The proceedings present the prevailing concepts of hormonal relationships, serving as an impetus for further investigations. Estrogens, androgens, and their derivatives received the greatest attention, although consideration was also given to the thyroid and gonadotropins.

The main papers are well organized and excellently presented and the informal discussions which followed are frank, provocative, and stimulating, and contribute a great deal to the value of the Conference. This book is highly recommended reading for those interested in the medical aspects of gerontology.

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MEDICAL PROBLEMS OF OLD AGE, by A. N. Exton-Smith. John Wright & Sons Ltd., Bristol, 1955, 331 pages 30 s.

This book may be considered a textbook in internal medicine with special emphasis upon the influence of age as far as the natural course of diseases is concerned.

The first chapters deal with the various diagnostic problems involved in diseases during senescence. Thereafter follow prophylaxis, medical care, and rehabilitation of old people living at home. The author mentions the risk involved in keeping old patients, who finally are to be discharged, in hospital for too long time, as the relatives may lose interest in them.

A special chapter is devoted to the subject of nursing care, which is discussed in the light of the underlying medical problems, as is surgery and anesthesia in a following chapter.

A systematic clinical description is presented of the major geriatric diseases: coronary occlusion, cerebral and peripheral arteriosclerosis, bronchitis, and arthrosis. A thorough description is given of cervical spondylosis with its compression and atrophy of the medulla, which—according to modern concept—is considered responsible for many cases of vague and protean neurologic symptoms from the extremities.

The book is filled with good clinical observations on the pathoplastic influence of the senium, and is well suited for supplementary study in internal medicine for students and physicians.

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AGEING IN TRANSIENT TISSUES, Vol. 2, Ciba Foundation, Colloquia on Ageing, edited by G. E. W. Wolstenholme and E. C. P. Millar. Little, Brown and Company, Boston, 1956, 263 pages, $6.75.

The topics dealt with in this volume are diverse in nature but all concern the process of aging in transitory structures. Many gerontologists have had occasion to speculate about the relationship of the aging of individual cells or circumscribed masses of tissue to the aging of the organism. The Ciba Foundation has made it possible, through this volume, to learn what a number of authorities, in prepared papers and in open dis-

cussion, have to say about the development and degeneration of transient structures.

In relation to normally transient fetal structures, such as the Wolffian ducts in the female, it is shown by study of explants that it is a hormone from the fetal testes which maintains these structures in the developing male embryo. It is shown also that testicular hormone stimulates the development of the primordia of the seminal vesicles and their further growth and differentiation and also causes an increase in the number of the prostatic buds. The testicular hormone diffuses through the explanted reproductive tracts and produces local effects. It is thought by the authors of this paper (Price and Pannabecker) that in the normal rat fetus testicular hormone may be effective by local diffusion as well as by circulatory pathways.

Additional information on endocrine factors operating in fetal development is given in the second paper by Jost. A study of the pituitary gland in the rabbit and of the testicular interstitial cells in man strongly suggests that endocrine glands pass through a period of maximal working at certain stages of prenatal life, followed by a period of lesser activity.

The third paper deals with the regeneration capacity of ovarian tissue (Zuckerman). Consideration of the duration of reproductive life in higher mammals, a knowledge that fertility reaches a peak in early maturity and then gradually declines, observation that the senile ovary cannot be reactivated by any known treatment with hormones, and various experimental data applying to the ability of the ovarian tissue to regenerate, lead the author to the conclusion that the ovary represents a transient tissue with relatively little regenerative capacity, not only in regard to its germinal but also to its secretory functions. The ovary is an organ which is more senescent or potentially more senescent than the male gonad, both from the germinal and from the secretory points of view.

Following up the study of the ovary as a transient type of tissue, the paper by Williams considers the history and fate of redundant follicles. Williams agrees with Zuckerman that all of the ovarian tissues are transient and that oogenesis is no longer a function of the ovary in adult life. In the discussion of this paper it was pointed out by Harrison that even cultures of granulosa cells persist for only a few days and that an addition of water-soluble estrogen to them will increase their lives for but a few days more.

The next paper (Rowlands) deals with the development and aging of the corpus luteum of the guinea pig. While the corpus luteum of the pregnant guinea pig grows for about 18 to 20 days and then is maintained at maximum size until parturition, histologic evidence shows that aging begins in mid-pregnancy. After parturition, regression is very rapid.

The paper by Fawcett and Burgos concerns observations on the cytomorphosis of the germinal and the interstitial cells of the human testis. The details of structure of the developing germinal cells and of the cells of Leydig as seen by means of the electron microscope are given. In relation to the question of aging, it is interesting to note that the evidence obtained by these authors indicates a probable transition of spindle cells into the Leydig cells. There is evidence also that the Leydig cells undergo an aging process, for some of them are seen to be crowded with lipid and pigment and to have greatly swollen and distorted mitochondria.

Dempsey deals with mitochondrial changes and concludes from the degree of change that mitochondria are definitely labile elements in the cell and frequently undergo marked changes in aging and in moribund cells as well as from physiologic activity.

An important segment of the book concerns various aspects of aging in the placenta. Wislocki has emphasized that the study of aging of the placenta is a matter of investigating not a single structural unit but a variety of organs which may function either successively or concurrently. While some placental structures are degenerating, others are growing and undergoing differentiation. Various placental structures are provisional or transient and serve for a short time to support the growing fetus. In the human placenta, for example, the chorion laeve and the decidua capsularis are provisional in nature and disappear completely by the fourth month of gestation.

Huggett points out in his paper that the placenta changes composition not in a regular sequence but in a spasmodic manner, suggesting that different functions are carried out at different ages and that the efficiency of some functions of this organ may even be increased in its old age. In fact, according to this author, we might think of the placenta as being expelled in its prime of life.

Villee considers the biochemical effects of aging in the placenta. One of the several interesting changes here is the gradual loss of ability of the placenta to secrete glucose. This is presumably due to the loss of the enzyme glucose-6-phosphatase. Thus in early fetal life the placenta may function to regulate the glucose content of the fetal blood stream but later in fetal life this function is taken over by the fetal liver. In all of the metabolic functions tested, the activity of the placenta decreases as gestation proceeds.

Studies on the uptake of radio-potassium (^{42}K) by the uterus and placenta in the rat and goat during the advancement of pregnancy (Harrison and D'Silva) indicate that there is no change in this function during the progress of gestation. The placentome is about 5 times as active in this regard as is the chorion. The authors have added observations on the morphologic changes in the placentas of these animals during the progress of gestation.

Studies by two French authors (Tuchmann-Duplessis and Mercier-Parot) concern the influence of STH (somatotrophic hormone) on the fetuses in several groups of pregnant rats. Administration of cortisone by these authors to pregnant rats slightly delayed embryonic development but almost completely arrested postnatal growth. Although the inhibition appears to be connected with disturbances of lactation, the great frailty of the offspring of the cortisone-treated mothers seems to indicate the existence of a more or less reversible change in their constitution.

The growth cycle of deer antlers (Wislocki) is presented as an example of development and age changes in transient structures. The growth phase of the antler cycle has been shown by this author to be initiated and completed in the spring and summer during a period of increasing and of maximum daylight, while the shedding of the velvet and rutting processes, indicating increased gonadal activity, occur in the autumn during

a period of diminishing daylight. A case of an individual stag is presented in which the sequence of events indicates the stimulating effect of withdrawal of light upon the differentiation of the antlers and on gonadal function (premature shedding of the velvet and rut) and the growth-stimulating effect of the increase of light by the subsequent resumption of antler growth.

Age changes in the axillary apocrine sweat glands in the human female (Montagna) include atrophy of the epithelium, presence of flocculent residue in their tubules, appearance of glycogen, and occasionally saliva-resistant Schiff-reactive granules. The most marked age changes in the axillary organ occur in the early fifties. Some elements always remain relatively normal in aging glands. Ovarian hormones play an obvious role in initiating the maturation and maintaining in part the functional state of these glands, but other hormones, perhaps from the cortex of the adrenal gland, are probably more closely implicated. In the aging male the glands show far less striking regressive changes than in the female.

Yemm points out that the predominance of catabolic changes in the senescent leaf tissue results at least in part from a decline in synthetic activity and not only from an increase in the hydrolytic break-down of the more complex constituents.

The last subject, which is treated in two papers, one by Lovelock and the other by Mollison, concerns the subject of aging of human red blood cells. In the first paper the interest attaching to storage as a means of extending viability is pointed out in relation to the red blood cell. The experimental results of study on the red blood cell offer confirmation for the idea that this cell is, in fact, a steady state system in which active synthesis maintains the cell at a constant composition in spite of the dispersion and disorientation of its substance by random molecular movement. The author points out that the inevitability of a process of senescence in such a system may be explained by use of the information theory (Shannon and Weaver, 1949). To preserve its identity in the face of wear and tear, a living cell must possess at its formation a considerable amount of information to direct the course of its repair functions. Whatever part of the cell has this information is itself, however, exposed to the destructive effects of random molecular movement and must eventually become too blurred to function. The salient feature in the paper by Mollison is the fact that ATP probably plays an important role in the maintenance of viability of normal red blood cells.

The general impression from these papers and the discussion of each one of them is that they have been presented with a large amount of interesting data and present much food for thought. On the other hand, there seems to be rather little unifying material running through the various papers. Perhaps this would be too much to expect. Much of the value of such a series of papers is of course contained in the discussion at the end of each one of them and in the general discussion which is placed at the close of the work.

To the gerontologist the question as to whether the term, aging, really is permissible in relation to such diverse subjects as the changes in transitory fetal structures, in the placenta, in red blood cells, and in deer antlers, is a very important one. While these are going through a process of development which continues on to a degenerative stage and to eventual dissolution, resorption, or casting off, as the case may be, we wonder how closely parallel to the process of the aging of an organism these changes are.

In the Discussion it is interesting to find the denial of the existence of certain processes, such as that of amitosis, on the grounds of what the reviewer cannot help but feel is a somewhat outworn prejudice, since he himself has observed all stages of this process in liver, salivary glands, and nervous system of senile organisms.

While the General Discussion is a stimulating section, it is somewhat discouraging to find, as so often is the case, a lack of clarity as to whether growth and differentiation are a part of aging and as to whether aging is different from senescence. It would seem time for some group, such as the International Association of Gerontology, to set up a series of definitions of such terms in the major languages to assist in our communication of scientific facts and concepts.

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BOOKS RECEIVED

Books received since August 1, 1956, are acknowledged in the following list:

Ageing in Transient Tissues, Vol. 2, Ciba Foundation, Colloquia on Ageing, edited by G. E. W. Wolstenholme and E. C. P. Millar. Little, Brown and Company, Boston, 1956, 263 pages, $6.75. (reviewed in this issue, page 62).

Body Measurements and Human Nutrition, edited by Joseph Brozek. Wayne University Press, Detroit, 1956, 170 pages, $3.50 (reviewed in this issue, page 62).

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DIFFERENTIAL CHANGES IN MENTAL ABILITIES IN OLD AGE*

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The decline of most mental test scores with advancing age is well known. The focus of contemporary research is not merely to redemonstrate this fact, but rather to discover patterns of differential decline (or growth) of factorially pure mental abilities in old age. The study by Schaie, Rosenthal, and Perlman (2) has reported such a pattern. These writers, employing Thurstone's Primary Mental Abilities battery (3) with 61 aged subjects, found a severe decline of reasoning and space abilities, moderate decline of word fluency, and minimal decline of number and verbal meaning. The research reported here attempts to replicate these findings and to explore the influence of a number of factors on test scores.

The manual containing the Thurstone tests presents the tests in a given sequential order. Particularly with aged subjects, it seemed likely that some effect associated with sequential order (e.g., fatigue or boredom) might contaminate the differential test scores reported by Schaie and associates (2). To test this possibility, a Latin Square experimental design was utilized in the present study. The design, by counterbalancing orders of presentation of tests, allows for the cancellation of order effects if such exist.

The decline of some test scores in old age may, as Schaie and associates have speculated, be attributable to a lack of recent practice of the abilities tested. Thus, abilities employed throughout life may hold up well, while those scarcely exercised since school days may deteriorate. To the degree that lowered test scores of aged subjects are attributable to lack of practice, their scores should improve with repeated administrations of the test. The early test administrations function as practice for the later tests. With this possibility in mind, each subject in the present study was tested on the same material on 4 separate occasions.

The decline of test scores in old age is often attributed in part to the difficulty in motivating aged subjects to perform well. We attempted to explore this factor by offering, before the fourth and final testing session, moderate cash prizes ($2.50) to those subjects who improved their scores markedly.

MATERIAL AND METHODS

There were 3 groups of subjects, with 25 subjects in each group. The institutional aged subjects were volunteers from a province-supported home for indigent old people; their mean age was 72.0, ranging from 54 to 85. The community aged subjects were volunteer members of a Senior Citizens Club, residing in their own homes; their mean age was 72.1, ranging from 65 to 85. The high school subjects, employed as controls, were volunteers drawn from the lowest quartile of their class standings. The subjects were all paid for their services.

There was no attempt to equate the groups exactly in terms of socio-economic or other variables. The institutional aged were unquestionably from a lower socio-economic and educational level than the community aged. The socio-economic and educational backgrounds of the high school subjects seemed roughly comparable to the community aged. We are, in any event, concerned not with *absolute* differences in test scores among groups, but with differences of score *patterning* as a function of age.

The test battery (5 tests) was administered to groups of 5 subjects. The entire battery was administered on 4 occasions to each group, separated by intervals of from 1 to 3 days. The full instructions were read aloud on each occasion, and on each day considerable individual attention was given to each subject to assure that the practice exercises preceding each test were successfully completed. The subjects, before the final testing session, were urged to do their best and told that the cash prize would be given to that member of the group whose scores improved the most. Information regarding results was never given.

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RESULTS

Effect of Order of Test Presentation.—The 2 groups of aged subjects were given the 5 sub-tests in a Latin Square design described by Edwards (1, p. 319). To allow comparisons among sub-tests, all raw scores were transformed to the percentile norms provided by Thurstone (4). Tables 1 and 2 summarize analyses of variance of the transformed test scores for the first testing session for the institutional aged and community aged groups. The analyses indicate, first, a significant effect of sub-tests. That is, differences between scores on the 5 sub-tests within the battery are significant. There is, however, no effect for either group either of sequence of presentation or of rank order of presentation. Thus, the significant differences among mean sub-test scores are *not* attributable to the orders in which the sub-tests have been administered.

Differential Changes in Abilities.—The fact that there is no effect of order but a significant effect of sub-tests suggests that the sub-test scores reflect a genuine differential pattern of changes in test scores with old age. The sub-test profiles for the first testing session, in terms of mean percentile scores, are shown graphically for all groups in figure 1. The mean percentile scores for all groups, all sub-tests, and all testing sessions are presented in table 3 .

The data indicate that the findings of Schaie and associates are, on the whole, replicated. The most severe deficit of the aged subjects is clearly in the space and reasoning sub-tests, while verbal meaning and number hold up best. The absolute scores of our subjects are considerably below those reported by Schaie and associates for their unselected sample, but the patterns of test scores are strikingly similar.

Effects of Practice.—Table 3 indicates a very clear tendency for all groups to improve with practice. That is, although the older subjects, as we speculated, show improvement with practice, a similar gain is shown by young subjects who presumably suffer from no deficit of recent practice in the tested abilities. The meaning of the improvement with practice is thus difficult to assess.

The role of rote memory in the practice effect is probably slight. The subjects were not told whether or not their answers were correct, and examination of the tests indicates that the space, reasoning, and number materials, at least, are not likely to be retained through rote memory.

TABLE 1. SUMMARY OF ANALYSIS OF VARIANCE OF TEST SCORES OF 25 INSTITUTIONAL AGED SUBJECTS.

Source	df	Mean Square	F	p
Sequence of presentation	4	177.4	—	—
Residual between individuals (error)	20	192.2	—	—
Sub-tests	4	178.8	3.43	.01
Rank order of presentation	4	42.3	—	—
Residual from Latin square (error)	12	90.9	1.74	—
Residual within individuals (error)	80	52.1	—	—

TABLE 2. SUMMARY OF ANALYSIS OF VARIANCE OF TEST SCORES OF 25 COMMUNITY AGED SUBJECTS.

Source	df	Mean Square	F	p
Sequence of presentation	4	405.0	—	—
Residual between individuals (error)	20	839.7	—	—
Sub-tests	4	1852.3	7.32	.01
Rank order of presentation	4	372.3	1.47	—
Residual from Latin square (error)	12	300.2	1.19	—
Residual within individuals (error)	80	253.2	—	—

TABLE 3. MEAN PERCENTILE SCORES OF ALL GROUPS ON ALL SUB-TESTS ON 4 CONSECUTIVE TESTING SESSIONS.

Sub-Test	Session 1	Session 2	Session 3	Session 4
Institutional Aged				
Verbal meaning	5.9	9.6	14.6	18.8
Space	2.8	2.9	3.2	4.5
Reasoning	2.0	1.4	2.3	3.2
Number	10.9	10.4	15.5	19.3
Word fluency	5.0	7.4	10.3	17.4
Community Aged				
Verbal meaning	23.0	32.3	41.5	44.4
Space	4.6	7.8	9.7	13.8
Reasoning	5.4	8.2	11.0	11.7
Number	28.9	48.3	51.5	54.2
Word fluency	16.1	26.3	29.9	45.6
High School				
Verbal meaning	29.9	42.1	50.8	57.3
Space	21.5	44.7	60.8	66.6
Reasoning	35.9	54.0	63.7	72.2
Number	56.4	66.5	68.0	73.0
Word fluency	31.8	63.6	82.7	91.7

The practice effect seems akin to the warm-up phenomenon, and may reflect the operation of such diverse factors as decreased nervousness and increased familiarity with the mechanics of marking answers in the proper spaces.

While it would be desirable to compare the magnitude of the practice effect across groups, this is difficult since the groups begin and remain at widely disparate levels of performance. Proportionally, at least, the older subjects seem to gain as much from practice as do the younger. The increase with practice among older subjects was sometimes particularly dramatic. Thus, one institutional aged subject, on 4 consecutive testing sessions, obtained percentile scores of 2, 16, 35, and 72 on the number sub-test. The same subject, on the verbal meaning test, obtained successive scores of 1, 38, 38, and 50. The aged groups—and particularly the institutional aged—contained, however, a good number of subjects who began with the extremely low scores and showed no improvement.

Table 3 also indicates that practice had little effect on the differential pattern of test scores. This is anecdotally illustrated by the performance of a community aged subject who, on the first testing session obtained percentile scores of 65 on verbal meaning, 7 on space, 3 on reasoning, 92 on number, and 95 on word fluency. The same subject on the fourth testing session obtained scores for the same tests of 98, 5, 10, 99, and 99. The subject dramatizes the severe deficit in the space and reasoning scores of the aged and illustrates as well the failure of these scores to improve much with practice.

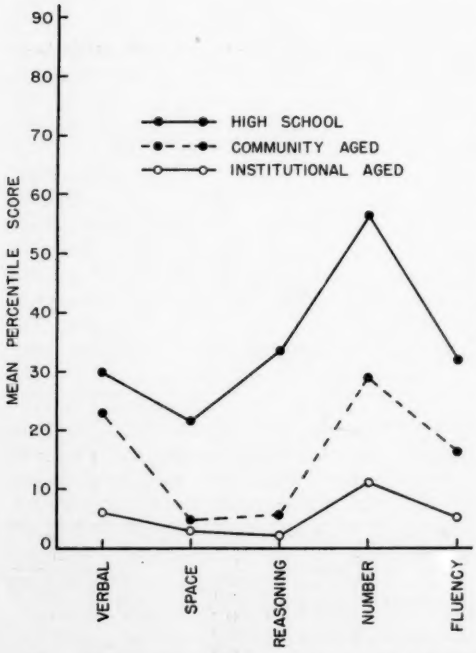

Fig. 1. Mean percentile scores on all sub-tests for all groups (first testing session).

The fact that at least some aged subjects show a marked improvement of some test scores with practice may be of significance for problems of personnel selection of aged people. That is, a single test administration may not reflect adequately the potential performance of an aged person. There were some aged subjects with very low scores on the first testing session who rapidly improved to the point where their scores surpassed those, even after practice, of most younger subjects. The ability to improve scores with practice, rather than the initial score, might be critical for some placement problems.

Effects of Increased Motivation.—The improvement of performance on the fourth testing session cannot be attributed solely to our attempt to increase motivation with a cash incentive. Performance during the fourth session also reflects the benefit of practice effects from the third session. There were, however, signs to indicate that, at least for *some* aged subjects, the level of motivation was markedly increased during the fourth testing. Perhaps the best indicator was performance on the word fluency test. This test requires the subject merely to write as many words as he can which begin with the letter s. The test on a priori grounds seems more sensitive than the others to heightened motivation. There were several aged subjects who showed very little improvement in this test during the first 3 sessions, but whose scores rose abruptly on the fourth (motivated) session. The percentile scores for this test for 6 selected aged subjects on 4 consecutive testing sessions were: 19-30-28-61; 5-5-10-76; 1-5-8-82; 8-6-10-85; 0-0-0-5; 30-23-15-85. The first 4 of these subjects were from the community aged, and the remaining 2 from the institutional aged.

The abrupt rise in score when an incentive was introduced, combined with the failure to achieve much improvement solely as a result of practice, suggests that the motivation of *at least these 6 subjects* was substantially affected by

the offer of a cash prize.* While it thus seems clear that heightened motivation could and did affect scores of *some* aged subjects on the fluency test, there is no good evidence that motivation affected performance on other tests. The scores, for the *same 6 highly motivated subjects* cited above, on the third and fourth sessions of the verbal meaning test were: 89-98; 41-56; 25-20; 8-25; 28-48; 15-13. The scores for the same subjects and same sessions on the space test were: 17-12; 2-5; 1-1; 0-0; 12-6; 0-0. The scores for the same sessions on the reasoning test were: 57-27; 14-10; 1-2; 1-0; 1-1; 1-1. The scores on the number test were: 87-95; 98-93; 2-2; 9-7; 16-16; 45-50. There is obviously no beneficial effect of added motivation on scores in the space, reasoning, and number tests. The small improvements in verbal meaning scores are in line with similar improvements made by the same subjects over the first 3 sessions, and are thus not unambiguously attributable to increased motivation.

The number of subjects on which this minute analysis is based is very small, but the data do suggest, first, that the performance of older subjects on *some* tests may be depressed by a failure to mobilize motivation, but, second, even when motivation is effectively mobilized, this does not in blanket fashion improve performance on *all* tests. The specification of what kinds of performances can be improved in aged subjects by adequate motivation is a problem of considerable theoretic and practical significance.

Factorial Purity of the Battery.—The 5 sub-tests in the PMA battery are described by Thurstone as factorially pure. The intercorrelations among sub-tests provided by Thurstone are, on the whole, satisfactorily low (4). These intercorrelations, however, were derived from standardization samples of young subjects. Possibly, the tests are not factorially pure for aged subjects, but Schaie and associates report, for their sample of aged subjects, intercorrelations "substantially lower" than those given by Thurstone.

Table 4 presents the intercorrelations among sub-tests for each of the 3 groups of 25 subjects. These are rank-order correlations, since some of the distributions were skewed. The table reveals that the intercorrelations are higher for both aged groups than for the high school students. The community aged display, in *each* of 10 possible comparisons, a higher intercorrelation of sub-tests than do the high school students, while the institutional aged display higher correlations in 9 of 10 comparisons. The correlations obtained for the high school students roughly approximate the range of magnitudes reported by Thurstone for the standardization samples; but those obtained for our aged groups fall considerably short of "factorial purity," and are considerably at variance with those reported by Schaie and associates for their aged subjects.

TABLE 4. RANK-ORDER INTERCORRELATIONS OF SUB-TESTS FOR ALL GROUPS (FIRST TESTING SESSION).

Sub-Tests	Community Aged	Institutional Aged	High School
Verbal meaning—space	.49	.43	.30
Verbal meaning—reasoning	.56	.26	.20
Verbal meaning—number	.39	.52	.19
Verbal meaning—word fluency	.50	.13	.48
Space—reasoning	.32	.26	.03
Space—number	.29	.59	-.35
Space—word fluency	.45	.17	.06
Reasoning—number	.20	.42	.13
Reasoning—word fluency	.49	.37	.17
Number—word fluency	.47	.47	.25

The Schaie study, however, obtained both speeded and power (untimed) scores on all tests. The writers do not indicate whether the intercorrelations which they report were derived from the speeded or power scores. Presuming that they were derived from the power scores, they would understandably be considerably lower than those which we report. There is ample ground to expect that a series of *speeded* sub-tests, factorially pure for a young population, would be less pure for aged subjects, among whom a decline in speed of work can be presumed to affect all sub-test scores.

SUMMARY

Thurstone's Primary Mental Abilities test battery was administered 4 times to 2 groups of 25 aged subjects and to a group of 25 young subjects. The fourth testing session included an attempt to heighten subjects' motivation by offering a cash prize for improvement. There was no effect of order of sub-test presentation on sub-test scores, and the differences in mean sub-test scores within the aged groups were thus presumed to reflect differential changes in mental abilities with old age. The most severe deficits

* This kind of abrupt increase in fluency score during the fourth session was never observed among the high school subjects. This, however, may be attributable to the fact that by the time the cash prize was offered the high school subjects were already approaching a maximum ceiling of performance.

of aged subjects were in space and reasoning abilities, with lesser deficits in verbal meaning, number, and word fluency abilities.

The scores of aged subjects improved with successive test sessions, reflecting an effect of practice, but the scores of young subjects also improved. There was evidence that the attempt to increase motivation improved the scores of some aged subjects on the word fluency test, but other tests scores seemed unaffected by increased motivation.

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JUDGMENT OF TIME IN YOUNGER AND OLDER PERSONS*

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Time is a human concept. As far as we can determine, only man has a sense of time and death. A normal sense of time aids in our adjustment and is an important means of establishing contact with and controlling the material universe (3, 4). Investigators (2, 11, 12, 18, 19) have shown, for example, that a common symptom in mentally ill patients is a disturbance of the sense of time. The importance of objective time—the calendar and clock—can hardly be overrated as a galvanizing force in man's life. There is mounting evidence that judgment of objective time can be changed by emotional experiences and that psychologic attitudes can influence the way in which we experience time (6, 7, 9, 13, 14, 15, 16). Observations indicate that when we experience many stimulations from the external world or when a time interval is filled with interesting activity, objective clock time seems to move fast. On the other hand, it seems to hang heavy when we are bored and nothing is happening (8, 20).

Time bears a definite relationship to the concept of future. It is believed that many older persons, particularly those dependent on others for their well-being, are individuals who have little to look forward to. They are people essentially devoid of a real future—with minimal stimulations available to them. Along this line of thought, the hypothesis is predicated that the older person faced with a limited tomorrow will underestimate objective time, i.e., clock time will seem to move more slowly than it actually does. The main purpose of this paper is an investigation of the relation between objective clock time and subjective time perception in older institutionalized persons. The results will be compared with similar data from a group of young adults to whom the future represents realization of aims and goals.

METHOD

Subjects.—The subjects consisted of two groups. One group was composed of 40 white, male World War I veterans living at a Veterans Administration Domiciliary. None had ever been mentally disturbed or had any apparent incapacitating brain involvement. Their presence in the Domiciliary was due to physical illness and consequent inability to support themselves economically. The mean age of the group was 67.0 (SD $\pm$ 3.4) years; mean educational level, 7.5 (SD $\pm$ 2.2) years; and mean IQ (based on Shipley-Hartford Test), 99.1 (SD $\pm$ 12.2). The second group consisted of 39 white, male, Korean war veterans applying for clarification of their training objectives under Public Law 550 at a Veterans Administration Guidance Center. None had any apparent physical or emotional difficulties. Their mean age was 24.0 (SD $\pm$ 1.3) years; mean educational level, 11.7 (SD $\pm$ 1.5) years; and mean IQ (also based on Shipley-Hartford Test) 109.0 (SD $\pm$ 9.6). The groups are not so far apart on the variables of education and intelligence as it may seem. We should remember that a half-century ago the public school graduate held an educational achievement status equivalent to that of the present high school graduate. Also, the Shipley-Hartford Test tends to underestimate intellectual capacity in older persons because of its speed aspect.

Procedure.—The production method of temporal judgment was used. In this method, *S* is instructed to delimit operatively an interval (the judgment) of a given duration (the standard) stated verbally by *E* (1).

A judgment by *S* which is smaller than the standard will be referred to as an underestimation of the standard. This means that *S*'s subjective temporal units are smaller than the objective temporal units, or that his internal clock is faster than the external clock. The production method was utilized in contrast to those of reproduction and verbal estimation because it allows more accurate judgment—less scattering of scores and elimination of the tendency toward verbal rounding of the judged interval (2). Both groups of subjects were asked operatively to estimate time intervals of 30, 60, 180, and 300 sec. To increase reliability, 3 estimates were obtained for each time interval; the final score being the mean of these esti-

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mates. The subjects were also asked how they went about judging the time intervals and what "time" and the "future" mean to them.

RESULTS

Analysis of the data established that perception of the passage of time was relatively stable in both groups. Those individuals who underestimated the 30 sec. interval tended to do the same for the other time intervals. This agrees with the findings of Eson and Kafka (5). Nevertheless, there was a trend toward increasing estimation of the standard with regard to the longer time intervals of 180 and 300 sec. A retest of 16 of the younger subjects one month later showed a correlation of .77, indicating a good level of consistency in judgment of the time intervals.

Table 1 indicates that the older group significantly underestimates the standard for all 4 time intervals when compared with the younger group. It is worthy of observation that the scores of the younger group (as well as those, naturally, of the older group) themselves differ reliably (.01 level for 30, 60, and 180 sec.; .05 level for 300 sec.) from the standard itself for all 4 time intervals. This significant underestimation of the time intervals may reflect a general characteristic of time judgment or possibly may be a function of the temporal method of judgment.

In response to the question "What does time mean to you?," 53 per cent of the older group answered "no meaning," and "nothing to do;" 32 per cent replied "something to be used for your advantage;" and 15 per cent saw it as "a measure." A large majority, 85 per cent, of the younger group viewed it as "a period of accomplishment." When asked how they went about judging the time intervals, a substantial majority in both groups, over 75 per cent, stated that they used some variant of "counted to myself." The remainder utilized visual cues, e.g., fantasying a second hand going around on a watch. No reliable differences were evident between the group on this point.

TABLE 1. SIGNIFICANCE OF THE DIFFERENCES BETWEEN YOUNGER AND OLDER SUBJECTS ON JUDGMENT OF TIME INTERVALS.

Standard Time Interval (In Seconds)	Mean Judgment of Older Group (In Seconds)	Mean Judgment of Younger Group (In Seconds)	Significance of Differences Between Groups
30	18.4	25.4	.01
60	40.0	55.0	.01
180	133.6	162.4	.01
300	241.5	285.2	.01
Number of Cases...	40	39	

TABLE 2. SIGNIFICANCE OF THE DIFFERENCES BETWEEN OLDER PERSONS WITH POSITIVE OUTLOOK ON "FUTURE" AND "TIME" AND THOSE WITH NON-POSITIVE OUTLOOK ON JUDGMENT OF TIME INTERVALS.

Standard Time Interval (In Seconds)	Mean Judgment of Older Group with Positive Outlook (In Seconds)	Mean Judgment of Older Group with Non-Positive Outlook (In Seconds)	Significance of Differences Between Groups
30	18.6	18.3	N.S.*
60	46.7	37.8	.01
180	156.3	126.1	.01
300	261.4	234.9	.01
Number of Cases...	10	30	

* Not significant at the .05 level.

With regard to the meaning of the future, 55 per cent of the older group perceived it in negative perspective as a period of "waiting for the end." Twenty-five per cent, however, did view it as a time when "you reap the rewards of your past life" and "can get out of the hospital to do wanted things you never had a chance to before." As was expected, the great majority, 85 per cent, of the younger group saw it in positive vein as a period of time in life during which they would implement individual ambitions and purposes.

The data were examined to determine whether any connection existed between outlook on the future and time and the individual's time judgments. Table 2 discloses that those individuals in the older group who held a positive orientation, e.g., "take care of yourself and go on," "get a kick out of life as long as possible," "do something worthwhile in the time left me," judged the standard more accurately and with less underestimation than did the rest of the group. This was true at the .01 level for all the time intervals except the 30 sec. one. As would be anticipated, further observation also revealed that those individuals who came closest to estimating correctly the standard maintained a definitely more positive outlook on the future than did the remainder of the group.

TABLE 3. SIGNIFICANCE OF THE DIFFERENCES BETWEEN YOUNGER PERSONS WITH NEGATIVE OUTLOOK ON "FUTURE" AND "TIME" AND THOSE WITH POSITIVE OUTLOOK ON JUDGMENT OF TIME INTERVALS.

Standard Time Interval (In Seconds)	Mean Judgment of Younger Group with Negative Outlook (In Seconds)	Mean Judgment of Younger Group with Positive Outlook (In Seconds)	Significance of Differences Between Groups
30	23.5	25.8	N.S.*
60	46.0	56.5	.01
180	139.5	166.5	.01
300	278.0	286.5	N.S.
Number of Cases...	6	33	

* Not significant at the .05 level.

The data were additionally inspected to discover whether negative orientation toward time and the future in the younger group would be related to judgment of the time standards. Table 3 shows that the 6 younger individuals who visualized the future and time in negative vein significantly underestimated the standard at the 60 and 180 sec. time intervals when compared with those having a positive outlook. Although differences at the 30 and 300 sec. time intervals were not reliable, they were still in the predicted direction. As in the older group, those individuals most accurately judging the standard held an affirmative view on the future and time. This was almost to be expected since 33 out of the 39 subjects fell into the "positive" category. No significant differences were established in either group between persons underestimating and overestimating the time standards.

It is noteworthy that the mean judgments of the younger "negatives" were equal to or closer to the standard than those of the older "positives"—except for the 180 sec. time interval. Perhaps, the aging process itself may play a role in underestimating of objective time, at least as measured by the temporal judgment method. It would be interesting on this point to secure comparative data on a "successful" older group.

DISCUSSION

The results bolster the conception that personal experience of time can differ from objective man-made time. The significant difference observed in time perception between the younger and older subjects draws attention to a possibly neglected age difference which should be given more cognizance. What life seems to hold forth for the individual apparently plays a role in the changed evaluation of time passage for some older persons. This seems to be true for some younger persons as well. People who do not experience the future as a field of much potential activity tend to see clock time as moving more slowly than it does in reality. Although it never assumes broad proportions, a trend exists in both groups for an increasing number of individuals to overestimate the longer time intervals of 180 and 300 sec. Clock time is judged as going faster than it really is. This may shed some light on the commonly held notion that time seems to pass faster the older we get (10). If there is a tendency for man to overestimate longer intervals of time, obviously this will come into sharper focus the older we are. The older person has more to retrospect on. Shock (17) among others, has pointed out that a week represents a much longer part of life for the 10-year-old boy than for the 70-year-old man. Another consideration is that a valid difference may exist in our response to "anticipated" time as against "experienced" time. It should be kept in mind that other factors can produce changes in the evaluation of time. To mention a few: biochemical changes due to drugs, fever, head injury, constitutional differences, social class, hypnotic suggestion, attention and set, etc. The point is that outlook on the future also seems to function as an influencing factor.

SUMMARY

Using the production method of temporal judgment, a group of institutionalized older persons in their sixties significantly underestimated time intervals of 30, 60, 180, and 300 sec. when compared with a younger group in their twenties. This changed evaluation of objective time might be given more attention in dealing with older people. The general time underestimation noted in both groups may be a function of the method used.

There was a tendency toward increasing overestimation of the standard with regard to the longer time intervals of 180 and 300 sec.

Perception of the passage of time, other things being equal, seemed relatively stable.

Persons with a positive outlook on the future judged the time standard more accurately than

those with a gloomy perspective. The inference is that the older person with a legitimate self-projection into the future tends to have a more correct sense of objective time, which may increase the probability of better adjustment.

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TRENDS IN THE ECOLOGY OF THE AGED IN AMERICAN CITIES, 1940 - 1950*

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In a study of the ecology of Wichita, Kansas, in 1954 (1) it was apparent that a high proportion of aged individuals resided in the central area of the city while other outlying sections of the city were almost devoid of old people. In one central tract, 17 per cent of the population was 65 or older, while several peripheral tracts contained less than 1 per cent in this age bracket. Both the range of variation and the extent of concentration in the central area seemed somewhat greater than had been observed in most earlier studies in other cities.

This observation raised the questions: Did Wichita have a greater degree of such concentration than other cities during the same period of time? Was this concentration the product of a recent trend which might also be observed in other cities in 1950? Most of the published materials relating to the ecology of the aged in other cities utilized data from the 1940 census or earlier. Would these same cities show more marked concentration in 1950?

The ecology of the aged in cities is a subject which has not received extensive, systematic study. Only three of the standard texts in urban sociology so much as mention the subject, and one of them treats the subject in one sentence. Queen and Carpenter (3) reviewing the evidence for gradients in St. Louis in terms of miles from the center of the city say, "The relative number of elderly persons was highest in the first (mile) and lowest in the second, rising in the third and fourth, thereafter declining steadily but not greatly." Apparently this generalization was based on data from the 1930 census and originally published in 1935 (2). Using 1940 data, Quinn in his *Human Ecology* (4) found little systematic concentration of the aged and certainly no regular gradient in Cincinnati. Among the areas analyzed, he found the highest proportion of the aged in an older, high-rent area only recently invaded by lower income groups. However, the central business district had a slightly higher proportion of the aged than the city as a whole.

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Smith and McMahan (7) incorporate a few pages from McKenzie's *The Metropolitan Community* including simplified population pyramids for selected areas of Chicago in 1920. While no percentages were given in this or the original study, the pyramids indicated a high proportion of the aged in the transient hotel and Loop area and in the rooming house district.

The most extensive investigation of the subject of the ecology of the aged to date was performed by Schmid (5). In his study of Seattle he had found high proportions of the aged in 1940 in rooming-house districts adjacent to the central business district. Subsequently (6) he correlated the percentage of the population 60 and over with 10 other variables for 20 cities, again using 1940 data. He found little consistency in these correlations. In most cities, the percentage of the population 60 and over correlated positively with mean rent and median grade in school completed. However, two of the cities showed the opposite tendency; in Portland and Seattle significant negative correlations with rent and education emerged. He concluded that these opposite tendencies were primarily related to the proportion of the aged in the population of the city. In those cities in which the proportion of the aged was low, the aged tended to live in areas of higher socio-economic status and, on the other hand, in the cities with high proportions of the aged, such as Portland and Seattle, they tended to live in areas of low rent and low educational status.

From these studies, it is possible to draw only tentative conclusions regarding the ecology of the aged in American cities: 1) All suggest some tendency toward a concentration of the aged in the central areas of cities, in or adjacent to the central business district; 2) McKenzie's data suggest that the prime affinity of the aged population is to various types of multiple housing and this observation is not specifically contradicted in any of the other studies; 3) Schmid's data are equivocal, since his correlations were not related to any generalized pattern of cities, but only to covariance of the aged population

and other phenomena regardless of the general pattern of the cities; 4) All of these studies were based upon data from 1940 or earlier and attempted to discover patterns at that time; could it be that the patterns of residence of the aged in American cities were in the process of changing?

There were several ad hoc reasons for believing that the aged population might have become increasingly concentrated in the center of cities in recent years. Earlier a considerable proportion of the population of the areas adjacent to the central business district was comprised of young single males, presumed to be recent migrants to the city just getting a start in the occupational world and not yet having acquired family responsibilities. The high marriage rate of the 1940's and the younger age at marriage may have depleted the young and single segment of the population, with an earlier removal to other sections of the city where family-type housing was more plentiful and more desirable. This would tend to leave a higher proportion of old folks in the center of the city.

Governmental provisions for assisting veterans in purchasing housing have had rather marked effect on urban ecology. To a degree seldom apparent before, newlyweds and young families have been able to purchase new housing and successfully compete in the housing market with older, more established citizens, which has led to the development of new housing areas, usually on the outskirts of the city, inhabited almost exclusively by young families. This movement has tended to drain off the young adult population from other sections of the city, including the central area, and may have left, in consequence, an older population in those central areas.

We also hear of a tendency of the aged, the widowed, and the retired, to give up the family residence and move into apartments. If such multiple dwellings tend to be closer to the center of the city than single-family dwellings, such a movement, to the extent that it exists, would be inclined to draw the aged toward the center of the city.

With these considerations in mind, it seemed reasonable to hypothecize that the central areas of American cities were tending to become characterized by a greater proportion of old people. Given a specific time reference and stated in testable terms this general hypothesis breaks down into 6 specific propositions: 1) The aged population will constitute a higher proportion of the total population of the central areas of cities than the percentage of aged in the total population of those cities; 2) The number of persons 65 and over living in central areas of cities will have increased from 1940 to 1950; 3) The percentage of increase in the aged population living in the central areas will exceed the increase in the total population of those central areas; 4) The aged population will increase faster in the central area than in the city as a whole; 5) The percentage of aged in the population of the central areas will have increased more from 1940 to 1950 than the percentage of aged in the population of the cities as a whole; 6) The central areas will contain a larger proportion of the aged population of the cities in 1950 than they did in 1940.

Should all of these propositions prove true, we can with confidence assert the general proposition that from 1940 to 1950 there was a trend toward increased concentration of the aged in the center of American cities. Should one or more not prove true, the general proposition will have to be qualified accordingly.

SOURCES AND METHODS

Since detailed census information concerning small areas of cities is readily available only for those cities in which census tracts have been established, and since only in such cities do the internal census areas maintain consistent boundaries from one census to the next, these were the cities included in this study. For various reasons, not even all of the presently tracted cities could be included. Some were not tracted in 1940, hence comparable data were not available for that year. Some which were tracted in 1940 were dropped from the list for which census tract data were published. In still others it was discovered that tract boundaries had been changed in such a way as to invalidate the types of comparisons desired. Since our hypotheses relate to an over-all ecologic pattern of the total community, those cities which are merely suburban to other larger cities were excluded.

These considerations reduced the number of cities to be included in the study to 39. For these, comparable data were available and such data were believed to be relevant to the hypotheses of the study.

Since the hypotheses made repeated reference to "central areas" of cities, it became necessary to give some operational meaning to this con-

cept. After considering many alternatives, it was decided that the most relevant aspect of the central area as far as this study was concerned was the relative concentration of multiple-dwelling residential structures. The need then was to delimit the central area in which such concentration was greatest. In view of the wide variation among our cities in the proportion of multiple dwelling units in the total residential property, use of an arbitrary percentage was not possible. The measure had to be relative to the pattern of the particular city. Therefore, as a general guide, the central area was defined as those census tracts in and surrounding the central business district in which the percentage of multiple dwelling units was greater than the mean plus one standard deviation of the percentage of such dwelling units in all of the tracts of the city. Theoretically this should have included about one-sixth of the tracts in each city.

In most cities, this procedure brought out a rather clearly defined cluster of tracts in the central portion and it was only necessary to draw a line around those tracts which qualified and were contiguous to the central cluster. Noncontiguous tracts were not included. In a few cities, the pattern was so skewed that the mean plus one standard deviation exceeded 100 per cent. In these, by inspection and experimentation, an arbitrary percentage, usually in the high nineties, was utilized to elicit the pattern.

These central areas were established on the basis of the 1940 census and the same areas were maintained in 1950.

Once the central area was established for each city it was possible to proceed with the calculations indicated in the hypotheses. All figures used in this study were drawn from the census tract bulletins published by the Bureau of the Census.

OBSERVATIONS

Hypothesis 1 states, in essence, that to a measurable degree the central areas of our cities have become specialized as residential areas for the aged. The measurements which were used to test this hypothesis were the percentage of the total population of the central areas made up of persons 65 years and over compared with the percentage of the total population of the city who were 65 and over. These comparisons were made for both 1940 and 1950.

In general, this hypothesis was confirmed as indicated in table 1. In 1940, 32 of the 39 cities had higher proportions of the aged in the central areas than in the remainder of the cities, and in 1950, 30 of the cities showed this tendency. Twenty-nine of the cities showed this pattern in both years. In only 6 cities did the reverse pattern, a higher proportion of the aged in the city as a whole than in the central areas, hold consistently true in both years. The other 5 cities were inconsistent for the 2 years with 3 moving from a condition of greater concentration of the aged in central areas to a lesser concentration in 1950 and 1 increasing the relative concentration of the aged in central areas. In 1950, 12 cities had more than 1 out of 10 people living in the central areas who were 65 or older whereas in only 3 cities as a

TABLE 1. PERCENTAGE OF POPULATION 65 AND OVER IN CENTRAL AREAS AND ENTIRE CITIES, 39 CITIES, 1940 AND 1950.

Name of City	(A) Percentage of Population 65 and Over in Central Area 1940	(B) Percentage of Population 65 and Over in Total City 1940	(C) Percentage of Population 65 and Over in Central Area 1950	(D) Percentage of Population 65 and Over in Total City 1950
Akron, Ohio	6.5	4.8	8.1	6.7
Atlanta, Ga.	4.5	4.9	5.9	6.7
Austin, Tex.	7.4	5.8	10.6	6.6
Baltimore, Md.	6.1	6.5	6.9	7.4
Birmingham, Ala.	4.2	4.3	5.7	6.3
Buffalo, N. Y.	6.7	6.5	7.9	8.4
Chicago, Ill.	5.9	5.8	7.5	7.6
Cincinnati, Ohio	7.4	8.5	7.9	10.0
Cleveland, Ohio	6.0	5.4	6.7	7.8
Columbus, Ohio	8.2	7.7	9.3	8.8
Dallas, Tex.	5.5	5.2	7.6	6.1
Dayton, Ohio	9.5	7.2	9.4	8.1
Denver, Colo.	10.5	8.8	13.4	9.4
Detroit, Mich.	5.0	4.0	7.4	5.7
Duluth, Minn.	9.5	7.7	13.5	10.0
Flint, Mich.	7.1	4.4	9.9	6.3
Houston, Tex.	5.1	4.3	8.0	5.0
Indianapolis, Ind.	9.2	7.4	9.9	8.7
Kansas City, Mo.	8.1	7.9	9.9	9.2
Louisville, Ky.	8.1	7.3	8.7	8.3
Memphis, Tenn.	5.8	5.5	7.8	6.6
Milwaukee, Wisc.	8.2	6.4	10.2	8.1
Minneapolis, Minn.	9.1	7.6	11.6	9.6
New Orleans, La.	6.1	5.9	7.9	7.1
New York, N. Y.	6.3	5.6	8.7	7.7
Oklahoma City, Okla.	7.2	5.3	10.5	7.0
Philadelphia, Pa.	6.8	7.0	8.1	8.3
Pittsburgh, Pa.	5.9	6.3	8.5	8.3
Portland, Ore.	11.5	9.4	16.0	11.0
Richmond, Va.	6.3	5.9	8.3	8.0
Rochester, N. Y.	9.1	8.2	12.2	11.0
San Francisco, Calif.	9.1	8.2	11.2	9.6
Seattle, Wash.	10.4	8.8	13.6	10.2
St. Louis, Mo.	6.7	7.6	7.7	9.4
St. Paul, Minn.	9.1	7.4	10.9	8.8
Syracuse, N. Y.	8.1	8.0	9.7	9.5
Toledo, Ohio	8.9	7.3	10.5	9.4
Trenton, N. J.	8.9	6.5	9.4	8.3
Washington, D. C.	6.3	6.2	7.7	7.1

whole did the aged have so high a ratio in the total population. One out of 6 persons in the central area of Portland was 65 or older, and almost 1 out of 7 in Seattle. It seems then that we can say that to a measurable extent the central areas of most cities have become specialized as dwelling areas for the aged and that, in general, Hypothesis 1 is confirmed.

Hypothesis 2: The number of the aged population living in the central areas increased in all 39 cities from 1940 to 1950, the increase ranging from 6 per cent in Houston to 46 per cent in Birmingham. It may be significant that it was in Birmingham that Schmid found the least tendency for the aged to live in areas of low socio-economic status. The present study suggests that this pattern may be in the process of change in that city. However, since all of the cities showed an increase in the numbers of aged in the central areas it must be stated that Hypothesis 2 was resoundingly confirmed, as shown in column A of table 2.

TABLE 2. CHANGE IN TOTAL POPULATION AND AGED POPULATION IN CENTRAL AREAS AND ENTIRE CITIES, 39 CITIES, 1940-1950.

Name of City	A Percentage Increase in Number of Persons 65 and Over in Central Area 1940-1950	B Percentage Change in Total Population of Central Area 1940-1950	C Percentage Increase in Persons 65 and Over in Total City 1940-1950	D Index of Increase of Aged in Central Area to Increase of Aged in Total City (A/C X 100)
Akron, Ohio	29.3	+ 3.5	58.0	50.5
Atlanta, Ga.	34.9	+ 2.8	50.0	69.8
Austin, Tex.	22.0	−14.3	72.0	30.6
Baltimore, Md.	9.2	− 2.0	26.2	34.9
Birmingham, Ala.	46.6	+ 6.9	77.7	59.9
Buffalo, N. Y.	35.5	+17.4	29.7	119.7
Chicago, Ill.	38.1	+ 8.0	38.9	97.9
Cincinnati, Ohio	16.2	+ 7.7	30.1	54.0
Cleveland, Ohio	36.0	+ 8.2	49.0	73.5
Columbus, Ohio	24.7	+19.1	39.7	62.4
Dallas, Tex.	23.9	−10.6	74.7	32.1
Dayton, Ohio	44.4	+ 5.6	29.0	153.4
Denver, Colo.	17.0	− 8.0	38.1	44.6
Detroit, Mich.	42.1	− 4.4	62.7	67.1
Duluth, Minn.	36.3	− 4.5	33.8	107.6
Flint, Mich.	34.4	− 4.3	56.5	61.0
Houston, Tex.	6.2	+31.8	80.9	7.6
Indianapolis, Ind.	9.2	+ 2.2	30.1	30.6
Kansas City, Mo.	26.3	+ 2.4	34.6	75.9
Louisville, Ky.	19.8	+12.9	30.7	64.3
Memphis, Tenn.	32.8	− 2.0	63.4	51.7
Milwaukee, Wisc.	38.5	+11.8	38.6	99.8
Minneapolis, Minn.	28.5	+ 1.2	33.4	85.3
New Orleans, La.	27.0	− 1.7	40.4	66.8
New York, N. Y.	44.0	+ 3.7	46.0	95.6
Oklahoma City, Okla.	17.5	−19.3	56.3	31.1
Philadelphia, Pa.	21.9	+ 2.6	26.0	84.4
Pittsburgh, Pa.	31.2	− 8.8	33.7	92.7
Portland, Ore.	29.0	− 7.1	43.8	66.2
Richmond, Va.	27.7	− 2.7	61.3	45.2
Rochester, N. Y.	32.4	− 0.9	37.0	87.7
San Francisco, Calif.	32.4	+ 7.8	43.2	75.0
Seattle, Wash.	33.4	+ 2.1	47.9	69.7
St. Louis, Mo.	25.2	+ 9.4	29.9	84.3
St. Paul, Minn.	20.9	+ 1.7	28.9	72.3
Syracuse, N. Y.	23.7	+ 3.2	26.3	90.3
Toledo, Ohio	26.4	+ 7.0	38.3	69.0
Trenton, N. J.	16.1	+10.6	31.0	51.9
Washington, D. C.	17.5	− 3.6	37.6	46.6

The third hypothesis was also confirmed, although one city proved an exception. In 15 cities the total population of the central areas actually decreased, as shown in column B, table 2. In these cities, the aged population not only increased faster than the total population, but the aged population continued to increase while the total population of the areas declined. In 23 other cases, the increase in the aged population was greater percentagewise than the increase in the total population. For several of these, the increase in the numbers of the aged was enough to account for the total increase. In the one exceptional case, Houston, which had the lowest percentage of increase in the aged population and the highest percentage of increase of the total population of the central area, the percentage of increase in the aged population was less than for the total population. However, since 38 of the 39 cities supported the hypothesis, it may be taken as a general principle that the aged population tended to increase in the central areas at a faster rate than the total population of the areas.

Hypothesis 4, that the aged population increased faster in the central areas than in the city as a whole, was not confirmed. In only 3 of the 39 cities did the percentage of increase in the aged population in central areas exceed the rate of increase of the aged in the cities as a whole, as shown in column D, table 2. Furthermore the aged population in all of the central areas of the 39 cities combined increased only 26 per cent while the aged population in the total population of these cities increased by 36 per cent. And even this latter percentage was less than the rate of increase (46 per cent) shown in the entire urban population of the United States.

Two factors may have operated to distort these results. On the one hand, the rigidity of the limits of the central areas, which were established on the basis of the pattern of multiple housing in 1940 and held constant to 1950 in order to maintain comparability, may have operated to limit the possibility of in-

crease relative to the rest of the city. If the central areas had been redefined on the same basis in 1950, it is possible that they would have expanded in territory. However, it did not seem possible in this study to permit any modification of the boundaries of the central areas and at the same time maintain any meaningful comparability of data. On the other hand, the city limits were expanded in more than half of the cities. This should have had the effect of raising the ratio of increase in any segment of the population, including the aged, as compared with the rate of increase in an area the boundaries of which were fixed. However, this factor alone cannot account for the result, for when we considered those cities in which the political limits were not altered we still found the same tendency. Therefore, Hypothesis 4 must be rejected.

Hypothesis 5 was that the proportion of the aged in the population of the central area increased more than the proportion of the aged in the population of the city as a whole. To test this proposition, an index number was constructed which was a composite of two prior index numbers. First, the percentage of the population of the central area which was 65 and over in 1950 was divided by the percentage which was 65 and over in 1940. Next, the percentage of the population of the city as a whole which was 65 and over in 1950 was divided by the percentage which was in that age bracket in 1940. Then the quotient in the first operation was divided by that of the second and multiplied by 100. This gave an index number which can be interpreted as follows: If the index number is above 100, the ratio of the aged in the central area increased more than in the city as a whole. If the index number is below 100, the ratio of aged population in the city as a whole increased more than in the central areas.

As will be seen in column A of table 3, this index exceeded 100 in 19 of the cities and was below 100 in 20 cities. In other words, in only half of the cities did the proportion of the aged population in the central areas increase more than the aged proportion in the entire cities. With these equivocal results we must say that the hypothesis was not confirmed.

The sixth hypothesis, that the central areas would contain a larger proportion of the total aged population of the city in 1950 than in 1940, was also not confirmed. In fact, the evidence in column B, table 3 points strongly in the opposite direction. In only 4 cities did the actual proportion of the aged living in the central area increase; in the other 35 cities there was a smaller proportion in the central areas in 1950 than there had been in 1940. The same two factors which were cited in the discussion of Hypothesis 4 may have operated to distort the results here, namely, the rigidity of the central area boundaries in the face of real expansion of the district in which the aged predominated and the expansion of the city limits. However, the latter factor seems not to explain the variation since, in those cities in which the political limits remained unchanged, the same trend emerged. This would seem to indicate that the first of these two factors may have exercised a strong influence in producing these results.

TABLE 3. CHANGE IN PROPORTION OF AGED IN THE POPULATION OF CENTRAL AREAS IN RELATION TO ENTIRE CITIES, 39 CITIES, 1940-1950.

Name of City	(A) Index of Relative Increase in Proportion of Aged in Central Area	(B) Increase or Decrease in Percentage of Aged Living in Central Area 1940-1950
Akron, Ohio	88.7	— 4.93
Atlanta, Ga.	96.0	— 1.71
Austin, Tex.	124.8	— 5.36
Baltimore, Md.	99.2	— 6.94
Birmingham, Ala.	93.8	— 3.15
Buffalo, N. Y.	91.8	+ 0.47
Chicago, Ill.	97.4	— 0.05
Cincinnati, Ohio	91.8	— 2.82
Cleveland, Ohio	77.2	— 1.12
Columbus, Ohio	98.9	— 1.74
Dallas, Tex.	117.1	—10.39
Dayton, Ohio	88.8	— 4.93
Denver, Colo.	118.7	— 3.73
Detroit, Mich.	104.0	—18.15
Duluth, Minn.	110.3	+ 0.63
Flint, Mich.	96.6	— 3.27
Houston, Tex.	133.4	— 4.37
Indianapolis, Ind.	90.6	— 4.55
Kansas City, Mo.	104.8	— 0.90
Louisville, Ky.	94.5	— 1.99
Memphis, Tenn.	112.1	— 5.85
Milwaukee, Wisc.	96.9	— 0.01
Minneapolis, Minn.	101.6	+ 0.26
New Orleans, La.	106.1	— 1.51
New York, N. Y.	100.7	+ 0.40
Oklahoma City, Okla.	111.1	— 6.72
Philadelphia, Pa.	101.1	— 2.01
Pittsburgh, Pa.	108.5	— 0.35
Portland, Ore.	118.2	— 2.37
Richmond, Va.	97.0	— 6.55
Rochester, N. Y.	99.8	— 0.74
San Francisco, Calif.	104.7	— 3.39
Seattle, Wash.	112.0	— 2.81
St. Louis, Mo.	92.3	— 0.75
St. Paul, Minn.	99.8	— 1.38
Syracuse, N. Y.	101.7	— 0.68
Toledo, Ohio	91.8	— 1.70
Trenton, N. J.	82.2	— 1.49
Washington, D. C.	107.2	— 7.49

SUMMARY

We may conclude that the central areas of most cities do contain a higher proportion of aged relative to the local population than the proportion of the aged in the population of the outlying areas of the cities. In this sense, the central areas are to a degree specialized as residential districts for older people. And during the decade 1940 to 1950 the aged increased in these areas both in number and in relation to the rest of the population living there. However, so great was the increase in the number and proportion of the aged in the general urban population that for most of the cities the rate of increase in the total city exceeded that in central areas and the proportion of the aged living in such central areas declined. Thus, while the central areas are to a degree specialized as residential areas for aged folk, the degree of such specialization in relation to the rest of the city is not increasing, and, in fact, shows some tendency to decline.

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FACTORS AFFECTING THE SELECTIVE USE OF A SOCIAL CLUB FOR THE AGED

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The wide general agreement on the value of social activities in the amelioration of certain physical and emotional involutional changes in the elderly has been adequately documented (1, 2). A recurring problem which accompanies the provision of services for the elderly, however, is attracting the persons for whom they are planned (5). Data on the personal activities of older persons have been gathered (4), but the problems of motivation and choice in the use of social centers have been approached only slightly. In considering the total problem of aging in the community, facts regarding those persons who choose not to use the existing facilities, as well as those who do, are important in the planning of additional centers (3).

MATERIAL AND METHODS

In the summer of 1952, the Community Mental Health Research Unit of the New York State Department of Mental Hygiene undertook a survey of all persons aged 65 years and older in 6 of the 61 census tracts in the City of Syracuse.* The primary focus of the interview was a social and mental health evaluation and the study areas were selected with this purpose in mind. In the outline of the hour-long unstructured interview there were questions relating to knowledge and use of the Wagon Wheel, a social club exclusively for the aged sponsored by the Corinthian Foundation, Inc. The information obtained is not the full picture of the use of social club facilities in Syracuse, since two other such clubs are available and information as to their use was not obtained.

Of the 1,807 persons in the age group 65 and over living in the 6 census tracts in the summer of 1952, personal interviews with replies to questions on the Wagon Wheel were obtained from 1,436, or 79.5 per cent. Of this number, approximately two-thirds said that they had heard of the Wagon Wheel; one-third said that they had not heard of it.

RESULTS AND DISCUSSION

Only 72 persons, however, or five per cent of those replying to the questions, reported that they had attended an activity of the Club at some time. Another group of 78 individuals, or 5.4 per cent, said that they might be interested and expressed a desire to know more about it (table 1). A total of 371, or 25.9 per cent, said that they could not or would not be interested in attending for some specific reason such as "too far," or "do not like that type of activity." In 58.2 per cent, the respondents indicated that they were not interested, but gave no specific reason for the lack of interest. Included in this category are such statements as "not for me," "nice for others" and "O.K. for those with nothing else to do." The remaining 5.5 per cent stated that they were physically unable to attend.

As might be expected, the answers for those who had not heard of the Club before the interview tended to be less specific than the answers from those who had previously known of its existence. As shown in table 1, 70.8 per cent of those who had not heard of the Club indicated a lack of interest and offered no explanation for the lack of interest, whereas only 50.9 per cent of those who had heard of the Club were in this category.

Of the 1,436 replies to these questions on the Wagon Wheel, 622 were from men and 814 were from women (table 2). Approximately two-thirds of the respondents were between 65 and 74 years of age; one-third were 75 or more years old. There were no important differences in the age distributions of the men and women.

As might be expected, men in the younger age group between 65 and 74 years of age showed the least interest in the Wagon Wheel activities. Only 6.7 per cent of this group had either attended the Club or indicated that they were interested in knowing more about it (table 2). The comparable figure for women

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* Syracuse City is composed of 61 census tracts. From these, two census tracts were selected which showed mental hospital first admission rates between 1935-1944 for persons 65 years of age or older that were among the highest in the city. Four additional tracts which showed low rates were selected for comparison. These high rate areas were concentrated in the center of the city.

TABLE 1. ATTENDANCE AT SOCIAL CLUB FOR THE AGED. SURVEY OF PERSONS AGE 65 AND OVER IN SIX CENSUS TRACTS. SYRACUSE, N. Y., 1952.

Replies	Total		Knew About Club		Did Not Know About Club	
	Number	Percentage	Number	Percentage	Number	Percentage
Total replies	1436	100.0	909	100.0	527	100.0
Had attended	72	5.0	72	7.9	—	—
Had not attended:						
Not interested						
Specific reason	371	25.9	267	29.4	104	19.7
Non-specific reason	836	58.2	463	50.9	373	70.8
Interested	78	5.4	57	6.3	21	4.8
Physically unable	79	5.5	50	5.5	29	5.5

between 65 and 74 years of age was 12.5 per cent; for men 75 and over, 11.8 per cent; and for women age 75 and over, 10.9 per cent.

The interest of the women in each age group, however, seemed to be slightly more active than that of the men, since more than half of the women expressing an interest had actually participated in its activities, as compared to only one-third of the men. In absolute numbers, 55 of the 72 respondents who said that they had attended the Club were women; only 17 were men.

Similarly, more women than men in the corresponding age groups had known about the Club before the time of the interview (table 2). In the other direction, however, it is interesting to observe that relatively more women than men in the same age group thought that they were not physically able to go to the Wagon Wheel. In the age group, 65 to 74, 5.6 per cent of the women were in this category as compared to only 1.2 per cent of the men; in the 75 and over age group, 10.6 per cent of the women made such a reply as compared to only 7.8 per cent of the men.

The comparison of the replies from the two age groups was somewhat as might be expected. The proportion of men expressing an interest in the Club increased with age; the proportion of both men and women who did not know about the Club increased with age; and the proportion who thought that they were physically unable to attend increased with age.

Similar data are presented for each census tract in table 3. There also are shown (a) the socio-economic levels of each tract, based on the sociologic indices of rent, home value, education, occupation and dwelling structure type, as reported in the 1940 census and (b) the estimated public transportation time required for travel from the center of the census tract to the Club. One of the three census tracts with sub-standard socio-economic levels (less than 95.0) includes a city housing project, located in Tract 42. The residents of this project are selected on the basis of financial need with priority assigned to family groups. Therefore, relatively few of the older people in this area live by themselves. Attendance at the Wagon Wheel was reported in 12.0 per cent of the replies from the housing project.

Census Tracts 41 and 42 (exclusive of the housing project) are immediately adjacent to the housing project, and are considered slum areas with relatively large numbers of transients, sub-standard housing, multiple dwelling structures, crowding and low educational and occupational levels. Prior attendance at the Wagon Wheel was indicated in only 7.1 and 2.6 per cent of the replies from these two areas, respectively. The meaning of the statistically significant difference in the frequency of reported attendance at the Wagon Wheel from these presumably similar tracts is not clear.

TABLE 2. ATTENDANCE AT SOCIAL CLUB FOR THE AGED ACCORDING TO AGE AND SEX. SURVEY OF PERSONS AGE 65 AND OVER IN SIX CENSUS TRACTS. SYRACUSE, N. Y., 1952.

Replies	Total	Age 65 to 74		Age 75 & Over	
		Male	Female	Male	Female
Total replies	1436	418	558	204	256
	Percentages of Total Replies				
Had attended and/or interested:	10.4	6.7	12.5	11.8	10.9
Had attended	5.0	2.4	6.6	3.4	7.0
Had not attended, but interested	5.4	4.3	5.9	8.4	3.9
Had not attended and not interested:	84.1	92.1	81.9	80.4	78.5
Knew about it	50.9	52.6	56.3	37.7	46.5
Did not know about it	33.2	39.5	25.6	42.7	32.0
Physically unable to attend	5.5	1.2	5.6	7.8	10.6

The remaining census tract in this group with low socio-economic levels (Census Tract 5) has a relatively large population of Italian origin. The lowest rate of attendance (1.9 per cent) was found in this tract. Differences in language as well as strong family and social ties in the neighborhood might account for the low interest and attendance from Census Tract 5.

Although differences in the age and sex compositions of the populations of each area have not been ruled out, the difference in utilization of the Wagon Wheel by the 4 areas with comparable low socio-economic levels (as measured by the index mentioned above), and comparable accessibility (as indicated by bus transportation time of 14 to 15 minutes) suggest that other factors may be important in determining interest of older persons in attendance at social clubs.

TABLE 3. ATTENDANCE AT SOCIAL CLUB FOR THE AGED ACCORDING TO CENSUS TRACT, SOCIO-ECONOMIC LEVEL OF CENSUS TRACT, AND PUBLIC TRANSPORTATION TRAVEL TIME. SURVEY OF PERSONS AGE 65 AND OVER IN SIX CENSUS TRACTS. SYRACUSE, N. Y., 1952.

Replies	Total[1]	Census Tract H.P. §	41	42†	5	27	18	49
Socio-economic index‡			91.4	89.6	88.0	98.8	104.4	106.6
Public transportation travel time (min.)		14*	14*	14*	15*	22*	5	22*
Total replies	1436	158	226	266	156	211	267	152
Percentage of Total Replies								
Had attended and/or interested	10.4	16.5	15.5	9.4	7.7	9.0	9.0	5.9
Had attended	5.0	12.0	7.1	2.6	1.9	3.8	6.0	2.0
Had not attended, but interested	5.4	4.5	8.4	6.8	5.8	5.2	3.0	3.9
Had not attended and not interested	84.1	75.3	77.9	83.5	87.9	85.8	87.6	90.8
Knew about it	50.9	50.0	47.4	39.5	27.6	61.1	65.5	60.5
Did not know about it	33.2	25.3	30.5	44.0	60.3	24.7	22.1	30.3
Physically unable to attend	5.5	8.2	6.6	7.1	4.4	5.2	3.4	3.3

* One bus change involved.

† Except for socio-economic index, exclusive of housing project shown in column H.P.

‡ Based on rent, home value, education, occupation, and type of dwelling structure as reported in the 1940 census.

§ Housing project.

TABLE 4. REASON REPORTED FOR LACK OF INTEREST IN SOCIAL CLUB FOR THE AGED. SURVEY OF PERSONS AGE 65 AND OVER IN SIX CENSUS TRACTS. SYRACUSE, N. Y., 1952.

Replies	Total	Census Tract H.P.†	41	42*	5	27	18	49
Total replies	1436	158	226	266	156	211	267	152
Had not attended and not interested	1207	119	176	222	137	181	234	138
Non-specific reason	836	78	111	154	94	137	174	88
Specific reason	371	41	65	68	43	44	60	50
Percentages of Replies with Specific Reasons								
No need	32.6	36.6	20.0	23.5	30.2	40.9	36.6	48.0
Dislike for type of activity	23.2	17.1	36.9	26.4	14.0	18.2	23.3	18.0
Too busy	19.9	19.5	15.4	22.1	34.9	18.2	21.7	10.0
Too far	7.3	9.7	12.3	5.9	4.6	6.8	1.7	10.0
Other unclassified	17.0	17.1	15.4	22.1	16.3	15.9	16.7	14.0

* Exclusive of housing project shown in column H.P.

In fact, only 27 individuals of the 1,207 who said that they had not attended and were not interested in attending the Wagon Wheel offered distance and difficulty in transportation as the reason for lack of interest. Only eight of the 27 lived in the census tracts farthest away from the Club.

The proportions in the other three tracts with higher social economic levels who said that they had attended the Wagon Wheel were 3.8, 6.0 and 2.0 per cent in Census Tracts 27, 18 and 49, respectively. Those who were interested but had not attended comprised 5.2, 3.0 and 3.9 per cent of the replies in the same census tracts, respectively (table 3).

It is interesting to note that among those who were not interested in the Club, relatively larger proportions had known of its existence in the census tracts with the higher socio-economic levels than in those with lower socio-economic levels (table 3).

Of the replies indicating a lack of interest, the proportions with no specific explanation ranged from two-thirds in Census Tract 41 to three-fourths in Census Tract 27 (table 4). Specific explanation accounted for one-fourth to slightly more than one-third of the replies indicating a lack of attendance and interest.

The statement most frequently offered in explanation of the lack of interest was "no need,"

or its equivalent (32.6 per cent), as shown in table 4. This reply was obtained from one-third of those who made a specific explanation of the lack of interest, ranging from 20 per cent in Census Tract 41 to 48.0 per cent in Census Tract 49. Except for the housing project, this answer was received more often in the areas with average or above average socio-economic levels (Census Tracts 27, 18, and 49) than in those with low socio-economic levels (Census Tracts 41, 42, and 5).

The next most frequent type of answer was "dislike for the type of activity." This answer or its equivalent was found in 23.2 per cent of those making a specific statement, ranging from 14.0 per cent in Census Tract 5 to 36.9 per cent in Census Tract 41. "Too busy" accounted for 19.9 per cent of the specific statements ranging from 10.0 per cent in Census Tract 49 to 34.9 per cent in Census Tract 5.

It should be noted that the reasons offered for a lack of interest in the Wagon Wheel were spontaneous statements resulting from an unstructured type of interview. "No need" was the most frequent or close to the most frequent reason stated in every area except Census Tract 41. This answer, together with "too busy" comprised 45 to 65 per cent of the reasons stated in six of the seven study areas. It is, of course, unknown whether similar distributions might have been found if all persons in the survey had been pressed for answers in a structured type interview. The similarity of the different socio-economic areas in this study, however, with respect to the large proportion of answers in the "too busy" and "no need" categories suggests that these figures may be applied to many different types of population.

SUMMARY

The Mental Health Research Unit of New York State Department of Mental Hygiene surveyed all persons aged 65 years or older in six Syracuse, New York, census tracts in 1952. Only a small percentage (5%) had attended the Wagon Wheel, a club for the aged, although an additional 5 per cent were interested, and two-thirds of the 1436 persons interviewed knew of the Club. Men in age groups 65-74 showed the least interest in the Club. Differences in both interest and attendance between areas showing variations in housing, economic and racial characteristics were found.

REFERENCES

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3. Laue, H. G.: A Community Plans a Recreation Program for the Aged. *J. Gerontol., 8:* 86-89, 1953.
4. Our Aged and What They Do: *Stat. Bull. Metropolitan Life Ins. Co. of Am., 32:* 5-7, 1951.
5. Swartz, F. C.: Problems Encountered in Setting Up a Rehabilitation Center. *J. Mich. Med. Soc., 52:* 511-512, 515, 1953.

BOOK REVIEWS

AGING: A CURRENT APPRAISAL, edited by Irving L. Webber. University of Florida Press, Gainesville, 1955, 179 pages, $2.50.

This most useful volume is a report of University of Florida's Sixth Annual Southern Conference on Gerontology. The program was planned to provide an overview of developments in the field during the preceding decade or so and to a considerable extent this was accomplished. Professor Hitt contributed an excellent review of population changes; Irving Lorge reviewed current data on intelligence and learning; Ruth Albrecht and William Harlan presented valuable papers on personal adjustment and attitudes toward the aging; Dr. Klein, Dr. Amato, and Professor Loftin surveyed physiologic and medical care trends; and Professor Spengler contributed a useful paper on financing an older population.

Several contributors, however, departed somewhat from the theme of the Conference. For instance, Halstead's paper on biological intelligence, Arnett's critical review of housing in Florida, and Alleger's exceedingly provocative results of Florida studies of older people on farms. The Conference and the book conclude with a far-reaching reexamination of institutional housing by Dr. Robert Kleemeier.

The entire book should be in the hands, or better in the minds, of all who are trying to incorporate emerging concepts into their programs.

CLARK TIBBITTS, Chairman
Committee on Aging
U. S. Department of Health,
Education, and Welfare

NEW CHANNELS FOR THE GOLDEN YEARS, the 1956 annual report of the New York State Joint Legislative Committee on Problems of the Aging, Legislative Document No. 33, 1956, 151 pages, paper bound.

This, the ninth annual report of the Committee headed since its beginning by Senator Desmond, contains, in addition to the official report to the Governor and the Legislature, articles by many prominent persons on several aspects of the problem of aging and copies of the bills passed by the 1956 Legislature, a few of which were vetoed by the Governor. Most of these bills were the results of the Governor's Conference held in October, 1955. *Charter for the Aging*, a report of that Conference, was reviewed in the July, 1956, issue of the *Journal of Gerontology*.

This report emphasizes "basic preventive measures which strike at the heart of the tragic, fundamental problems that beset our mature citizens," and lists four aspects on which the State should center its effort: The prevention of poverty in old age, the prevention of wastage of middle-age and old age, the prevention of needlessly rapid physical and mental deterioration, the prevention of inter-generational maladjustments.

Much of the activity in behalf of the aging, it says, has been concerned with day-to-day problems, with stop-gap measures such as providing recreation programs, but there should be a more fundamental approach with definite focus, direction and priority—long range goals.

New York has been making fundamental attacks on the problem, and has been an example to others. Most of the credit for its leadership goes to its long standing Joint Legislative Committee on Problems of the Aging, which has influenced action on all levels.

W. H. REALS
Washington University, St. Louis

SELECTED PAPERS OF JOSEPH W. MOUNTIN, M.D., edited and published by the Joseph W. Mountin Memorial Committee, 1956, available through the American Public Health Association, 1790 Broadway, New York, 356 pages, $5.00.

Dr. Mountin was one of the great pioneers of public health. Coming up through local and state health departments, he was well-acquainted with both needs and the deficiencies in practices; hence, was no arm-chair administrator. In his long but truncated career in the United States Public Health Service, Dr. Mountin was in a position to strike out boldly for advances and did. His *modus operandi* was to advocate from the platform and then to implement through studies and administrative procedures.

The memorial volume is, of course, a collection of Dr. Mountin's prolific stream of provocative writings. An examination of the table of contents reveals the tremendous range of his interest; community health organization; medical care in public health programs; supply and training of health personnel; regional development of public health services; multiple diagnosis screening; hospital development; grant-in-aid programs; housing. During the last years of his life (which ended abruptly with a cerebral accident in 1952), Dr. Mountin was working hard to get public health recognition of the problem of aging.

The papers are well worth reading because most of them set goals which are still far from attainment.

CLARK TIBBITTS, Chairman
Committee on Aging
U. S. Department of Health,
Education, and Welfare

BOOKS RECEIVED

Books received since August 1, 1956, are acknowledged in the following list:

Aging: A Current Appraisal, edited by Irving L. Webber. University of Florida Press, Gainesville, 1956, 179 pages, $2.50 (reviewed in this issue, page 85).

Canadian Welfare Council, 36th Annual Report, 1956, 16 pages, paper bound.

The Dynamics of Aging, by Ethel Sabin Smith. W. W. Norton & Company, Inc., New York, 1956, 191 pages, $2.95.

Five Hundred Over Sixty, a Community Survey of Aging, by Bernard Kutner, David Fanshel, Alice M. Togo, and Thomas S. Langner. Russell Sage Foundation, New York, 1956, 345 pages, $4.00.

Horizons for Older People, by George Gleason. The Macmillan Company, New York, 1956, 137 pages, $2.95.

Les Personnes Agées, in *Échanges*, No. 28, 16 rue St. J. B. de la Salle, Paris, 1956, 40 pages, 120 Fr.

New Channels for the Golden Years, 1956 report of the New York State Joint Legislative Committee on Problems of the Aging, Legislative Document No. 33, 1956, 151 pages, paper bound (reviewed in this issue, page 85).

Psychological Aspects of Aging, Proceedings of a Conference on Planning Research, Bethesda, Maryland, April 24-27, 1955, edited by John E. Anderson. American Psychological Association, Washington, D. C., 1956, 323 pages, $2.00.

Rehabilitation Trends—Midcentury to 1956. Institute for the Crippled and Disabled, 400 First Ave., New York, 1956, 95 pages, paper bound, $2.00 (special rate of $1.85 plus minimum handling and mailing charge of 20c to institutions purchasing 11 or more copies).

Retirement—A New Way of Life. University of Wisconsin, University Extension Division, Madison, 1956, 40 pages, 50c (40c each for 10 or more).

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Section C

Organization Section
Index to Current Periodical Literature

ORGANIZATION SECTION

Gerontological Society, Inc. Council for 1957

President	Robert J. Havighurst (Chicago)	Past President	William B. Kountz (St. Louis)
President-elect	Albert I. Lansing (Pittsburgh)	Treasurer	John Esben Kirk (St. Louis)
	Secretary	Nathan W. Shock (Baltimore)	

Biological Sciences	*to serve through*	*Psychological and Social Sciences*	*to serve through*
Henry S. Simms (New York)	1957	James E. Birren (Bethesda)	1957
Warren Andrew (Winston-Salem)	1959	Robert W. Kleemeier (Orange Park)	1959
Clinical Medicine		*Social Welfare*	
Arthur A. Hellbaum (Oklahoma City)	1957	Florence E. Vickery (San Francisco)	1957
Robert T. Monroe (Boston)	1959	Louis Kuplan (Sacramento)	1959

General Membership

Oscar J. Kaplan (San Diego) 1957
Walter M. Beattie, Jr. (St. Charles, Mo.) 1958

Past Presidents of the Society

William DeB. MacNider	1945	Clive M. McCay	1949	E. Vincent Cowdry	1953
Roy G. Hoskins	1946	C. J. Van Slyke	1950	Anton J. Carlson	1954
Lawrence K. Frank	1947	Robert A. Moore	1951	Ollie Randall	1955
Joseph C. Aub	1948	Ernest W. Burgess	1952	William B. Kountz	1956

SUMMARY OF THE MINUTES OF THE ELEVENTH ANNUAL MEETING OF THE COUNCIL AND MEMBERS OF THE CORPORATION OF THE GERONTOLOGICAL SOCIETY, INC.*

The meeting was called to order at 7:20 p. m. November 7, 1956, in the Chicago Room of the Hamilton Hotel, Chicago, Illinois. All members of the Council were present except Dr. J. Weil. Also present at the Council meeting were Dr. W. Andrew, Dr. E. V. Cowdry, Mr. L. Kuplan, Dr. A. I. Lansing, Mrs. L. Friedman, and Mrs. M. Adler.

The Minutes of the Tenth Annual Meeting of the Council and Members of the Corporation of the Gerontological Society, Inc. were approved. It was voted to publish a summary of the Council actions and the intent of the committee reports in the Journal of Gerontology.

Dr. Kirk presented a written report of the Treasurer, stating that while the financial situation of the Society for 1956 was fair, it was anticipated that additional funds would be needed to defray expenses for 1957. It is estimated that there will be a total deficit of about $256.00 this year and had it not been for the grant received from the Forest Park Foundation for 1956, the deficit would have been $3,756.00.

Dr. Shock, presenting the report of the Secretary, stated that there is a total membership of 1208 as against 1151 in 1955; 248 new memberships were received (188 professional, 60 general) and 191 memberships were discontinued because of deaths, resignations, and members in arrears in dues for two years. There are 1004 professional members in good standing, 124 general members ($2.50 dues) in good standing. On recommendation of the respective committees of each Section of the Society, 143 members were elected by the Council to Fellowship status.

The Council approved the appointment of a committee to develop uniform standards for Fellowship status, a member from each Section of the Society to be included in this committee.

The report of the Nominations Committee was presented by Dr. Cowdry, Chairman. Dr. A. I. Lansing was nominated as President-elect, and Dr. Kirk and Dr. Shock were nominated for Treasurer and Secretary, respectively. Dr. W. Andrew was nominated to replace Dr. J. A. Hamilton as Council representative of the Section on Biological Sciences, Dr. R. T. Monroe to replace Dr. J. T. Freeman as representative from the Section on Clinical Medicine, Dr. R. W. Kleemeier to replace Dr. Wilma Donahue as representative from the Section on Psychological and Social Sciences, and Mr.

* A full report is available upon application to the Executive Secretary, Mrs. Marjorie Adler, 660 South Kingshighway Blvd., St. Louis 10, Missouri.

L. Kuplan to replace Dr. J. Weil as representative from the Section on Social Work and Administration. It was recommended that the position of Executive Secretary be established and that Mrs. M. Adler be appointed.

Dr. Kirk presented a report of the Editor of the Journal of Gerontology, stating that subscriptions to the Journal of Gerontology (including membership subscriptions) totalled 1794 as of October 1, 1956, as compared with 1679 as of October 1, 1955.

Mr. Kuplan, Chairman of the Affiliate and Associate Groups Committee, presented an application for affiliation by the Western Gerontological Society. It was decided that members of affiliate and associate groups should be admitted to general membership in the Gerontological Society with annual dues of $1.50 per member and the right to vote at the Business Meeting of the Gerontological Society, a subscription to the Newsletter to be included. Individual membership cards will not be issued to individuals in this category, but their names will be included in the printed membership list whenever it is published.

In the report of the Editor of the Newsletter, Dr. Kaplan stated that the Newsletter continues to grow in circulation and influence and an increasing number of newsworthy items are received, some of which cannot be published because of the lack of funds for expansion of the publication.

The Council appointed Dr. Kaplan Editor of the Newsletter for a second term of three years, and referred the question of accepting advertising and its distribution within the framework of the Newsletter to the Newsletter Committee for consideration during the coming year. Dr. Kaplan's recommendation that the mailing of the Newsletter be transferred to the office of the Journal of Gerontology for the coming year was approved.

The Council accepted the recommendation of Dr. Freeman, Chairman of the Membership Committee, that some continuity of the Chairmanship of the Membership Committee be established and that the Chairman of this Committee for 1957 select key people in various geographic areas of the United States to be responsible for the promotion of memberships in their respective areas.

In accordance with the request of the Section on Clinical Medicine, a preliminary report was submitted by Dr. Commons, Chairman of the Committee to Investigate the Existence and Characteristics of Residencies and Clinical Training Programs in Geriatrics and Gerontology. The Committee found that of the 65 medical schools canvassed by questionnaire, two have departments of geriatrics and/or undergraduate elective courses in geriatrics or gerontology and that 3 schools reported postgraduate courses available for practicing physicians.

Specific standards for exhibits at the scientific meetings of the Society were drawn up by a committee under the chairmanship of Dr. Kirk and were accepted by the Council, together with the Committee's recommendations regarding the membership of the Committee and its duties.

Dr. Andrew presented the report of the Committee on Constitution and By-Laws. The Council recommended that each Section of the Society submit recommendations to the Council for representatives of their respective Sections on the Council as vacancies occur.

Dr. Lansing, Chairman of the Research Grants and Fellowships Committee, reported progress in the organization and selection of authors for the preparation of a critical review of the chemistry of the arterial wall to be made under a research grant from the Glendorn Foundation; the Committee is also planning several meetings to draw up recommendations of the needs in research and research training in gerontology to aid in the development of a policy for expanding research on aging.

At the request of the National Science Foundation for aid in screening applicants for NSF travel grants to the Fourth International Gerontological Congress in Italy, the Council authorized the Chairman of the Research Committee of the Society to appoint a sub-committee from its members to serve this function.

A contribution of $50.00 toward the work of the National Society for Medical Research was approved, and the meeting was adjourned at 11:30 p. m.

Continuation of Council Meeting—The meeting was called to order at 4:45 p. m., November 8, 1956, in the Flemish Room of the Hamilton Hotel, Chicago, Illinois. Members of the Council present were the same as indicated before; in addition, Dr. Lansing and Dr. Andrew were also present.

A summary of the Minutes of the Council Meeting of November 7 was read and approved as amended.

In view of the anticipated deficit for 1957, the Council recommended that the annual dues for Fellows and Members receiving the Journal be increased to $12.50 per year (for members residing in the U. S. A. and Canada). In addition, the Council voted to set the registration fee for the annual meetings at $5.00, with remission of the fee to bona fide students and invited speakers (non-members invited for symposia). The Council authorized the President to appoint a standing committee on finances to explore ways and means of increasing the income of the Society.

Dr. A. B. Chinn was appointed Chairman of the Committee on Local Arrangements for the 1957 meeting to be held in Cleveland* and Dr. Freeman was authorized to negotiate hotel arrangements for the 1958 meeting to be held in Philadelphia. The Council recommended that the 1959 meeting be held in Minneapolis and the 1960 meeting in Boston. It was suggested that consideration be given to holding the 1961 meeting in Los Angeles or Louisville.

The applications for affiliation with the Gerontological Society submitted by the Western Gerontological Society and the Florida Council on Aging were approved.

The Council accepted the recommendation of the Section on Social Work and Administration to change the name of this Section to Section on Social Welfare and authorized the appointment of a Committee to redraft the requirements for Fellowship status in this Section.

The meeting was adjourned at 6:05 p. m.

N. W. SHOCK, Secretary

* The dates of October 31 and November 1 and 2 were selected for the 1957 annual meeting of the Society to be held in Cleveland at the Hotel Cleveland. The 1958 annual meeting will be held in Philadelphia, November 6, 7, and 8, at the Hotel Bellevue Stratford.

SUMMARY OF THE MINUTES OF THE NINTH ANNUAL BUSINESS MEETING OF THE GERONTOLOGICAL SOCIETY, INC.

The meeting was called to order by President W. B. Kountz at 9:45 a. m., November 9, 1956, in the Mirror Room of the Hamilton Hotel, Chicago, Illinois.

The actions and recommendations of the Council (see above minutes) were reported by the President, Secretary, and Treasurer of the Society. The report of the Corporation was made available for inspection by members of the Society.

The nominees presented by the Council were unanimously elected, and after discussion from the floor, all actions and recommendations of the Council were approved (for details see minutes of the Council meeting).

The 1957 annual meeting will be held in Cleveland, Ohio, October 31, November 1 and 2. The 1958 annual meeting will be in Philadelphia and the 1959 meeting in Minneapolis.

N. W. SHOCK, Secretary

Reports from Foreign Correspondents

GERONTOLOGIC ACTIVITIES IN FINLAND

EEVA JALAVISTO

During the three years which have passed since the last report, (*J. Gerontol., 8:* 506-508, 1953) the developments of gerontologic activities in Finland have concerned both social, economic, and medical problems.

The difficulty in solving the housing shortage problem, which is very acute in Finland, is manifested also in the increasing need for institutional care of the old. To meet the requirements an almost incredible activity in building of new communal homes for the aged has started. The number of new homes since 1950 exceeds 140, and because the statutes require the plans for each home to be approved by the Ministry of Social Affairs, a relatively high standard has been maintained throughout.

In social legislation the year 1956 is worth notice, because a new Social Aid Act repealing the former Poor Law and a new National Pension Act were passed which will come into force in 1957. The latter Act signifies a complete change of principle; the old National Pension Act, which was in force since 1939, was based on the insurance principle, whereas the new act has more or less the character of a social aid program with old age pensions disbursed mainly from the collected payments (special tax) of that fiscal year. The old age pensions, which were highly insufficient, will be considerably increased, the amount dependent upon the age at retirement. For instance, if the old age pension commences later than at the age of 65, the basic pension will be raised by 12.5 per cent for each year of postponement beyond the age of 65. The maximum increase is, however, 62.5 per cent, payable if the pension is begun when the insured person is 70 years of age or more. The National Pensions Institution has also received permission to grant loans for building old peoples' homes, which was formerly not allowed.

In each Scandinavian country (Finland included) a permanent delegation for discussion of common problems of old age has been established. The Ministry of Social Affairs, the State Medical Board, communal old age and social aid institutions in Helsinki, the National Pension Institution, voluntary organizations, e.g., the Federation for Welfare of the Aged, Societas Gerontologica Fennica, and the Finnish Red Cross, which has lately also taken the care of the elderly into its program, are represented in the Finnish delegation. The fact that the Congress of Scandinavian Medical Officers of Health, held in Finland August 27-29, 1955, was entirely devoted to questions of old age and also that the annual two-day lecture courses dealing with various gerontologic topics arranged by the Federation for Welfare of the Aged were well attended indicate a growing interest in gerontology and geriatrics everywhere.

Research activity in gerontology is sponsored mainly by the Societas Gerontologica Fennica. In addition to the publication of the yearbook, *Geron,* (Finnish and Swedish, English summary) the Society has granted stipends for various research projects. The studies are being conducted mainly in its own Research Center for the Aged and Geriatric Outpatients Department and partly in other institutions, of which the City of Helsinki Communal Hospital (L. E. Tötterman, Chief) deserves special mention.

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GERONTOLOGIC ACTIVITIES IN DENMARK

TORBEN GEILL

The Danish Gerontological Society (Dansk Selskab for Alderdomsforskning) during the Spring of 1955 conducted a round table discussion on gerontologic problems in conjunction with the Danish Society of Internal Medicine. The participants were R. Friedberg (morbidity during the senium), H. Olsen (gerontopsychiatric problems), J. Clemmesen (cancer), V. Porsman (rehabilitation). P. From Hansen (gerontologic research), and T. Geill (the current status and future goals of gerontology). In April, 1956, a meeting on gerontology was held by the Danish Society of Internal Medicine. On this occasion T. Dalsgaard-Nielsen described the modern diagnostic procedures and the treatment of cerebral thrombosis and cerebral hemorrhage; T. Geill reported results of investigations on disturbances in blood coagulation in old subjects; P. From Hansen gave a survey of investigations on serum transaminase determinations in patients with coronary occlusion; and A. Hjorth and E. Møller-Christensen reported observations on successful treatment of urinary incontinence with testosterone proprionate in elderly women.

Plans for expansion of De Gamles By, the municipal geriatric hospital of Copenhagen, have been completed and the necessary funds for the construction of new buildings have been approved by the municipal authorities. After the scheduled expansion has been effected, the institution will have a capacity of 1800 beds, 1000 of which will be located in the hospital section. A modern rehabilitation department, new laboratories and therapy rooms, and a clinic for the handling of old patients with acute disease conditions, particularly coronary thrombosis, pulmonary embolism, and uremia, will be built.

Interest in geriatric hospital departments seems to be increasing in Denmark. The University Hospital of Copenhagen is considering establishing a geriatric department in connection with a professorship in geriatrics.

With regard to publications in the field of gerontology, the reviewer and S. Eckerström in 1955 published a textbook on geriatrics (reviewed in the Journal of Gerontology, *11:* 308, 1956). The book, which is intended for use by senior medical students and practicing physicians, is the first of its kind published in a Scandinavian language.

In the following paragraphs the investigations in the field of gerontology which have been carried out during the last two years will be mentioned. H. Dam, T. Geill, Erling Lund, and R. Søndergaard investigated the effect of various anticoagulants of the dicumarol type on old subjects. The authors found that preparations with a protracted action were to be preferred to drugs with shorter action. It was further demonstrated that in the case of serious hemorrhagic complications caused by overdosage with anticoagulants of the dicumarol type the prothrombin-provertin concentration (as determined by the Owren-Aas procedure) could be raised to the therapeutic range of 10 to 30 per cent by intravenous administration of 5 to 10 mg. of vitamin K_1 in aqueous suspension. The effect occurred 1 to 2 hours after the injection as compared with 6 hours following peroral intake of K_1. It was further found that in patients in whom a reduction of the prothrombin-proconvertin concentration to below 10 per cent was recorded, but who had not as yet developed hemorrhagic complications, an increase of the prothrombin-proconvertin level to within the therapeutic range could be effected by peroral administration of 1 to 2 mg. of vitamin K_1. In contrast to this, the water soluble vitamin K preparations of the menadione type were found to have an inconstant and weak effect, for which reason the use of this type of drugs in emergency cases must be considered inadvisable.

Comparative determinations performed by the Owren-Aas method and the Larsen-Plum procedure ("prothrombin time method") carried out on 765 blood

samples by the same investigators (Erling Lund, T. Geill, H. Dam, and R. Søndergaard) showed notable differences, especially in the case of samples with high values. This discrepancy may be due to the fact that the Larsen-Plum method reflects individual variations in the coagulation factors which are held constant in the Owren-Aas procedure.

A report on the clinical value of long term therapy with dicumarol in 17 patients was given by Erling Lund. Out of 68 patients who received short term treatment with anticoagulants 4 developed hemorrhagic complications.

T. Geill observed that elderly patients with liver cirrhosis developed thrombosis and embolism of the pulmonary arteries less frequently than other patients. In postmortem studies the incidence of thrombosis and embolism was found to be 11.5 per cent in elderly patients with liver cirrhosis as compared with 24.5 per cent in other patients. The lower incidence of pulmonary thrombosis and embolism among the cirrhosis patients can most probably be explained by a lower formation of thrombin. The thrombin determinations in these studies were performed by the thrombin generation test.

An extensive investigation on changes in skin temperature following injection of tetraethylammonium bromide has been carried out by H. Leschly-Jacobsen. Groups of patients with peripheral and universal vascular disease, especially arteriosclerosis, Buerger's disease, thrombosis and embolism of the arteries of the lower extremities, and Raynaud's disease were examined. Thermoelectric measurement on the dorsal aspect of the foot was found to be a valuable procedure for such studies. In patients with circulatory disturbances the temperature increase resulting from the tetraethylammonium bromide administration, when measured on the artificially cooled lower extremities, was found to be delayed and reduced; in severe cases a decrease in the skin temperature was even noted following the injection of the drug. The method seems useful for clinical application; the findings of the test showed a good correlation with the results of arteriography, and the procedure was clearly superior to that of oscillometry.

A. Norgaard reported the results of blood pressure measurements in 2269 elderly persons (age 70-91 years). All the subjects were physically active (held automobile driver's licences). In males between the age of 72 and 82 years the systolic blood pressure was found to be 156 $\pm$ 30 mm. Hg, and the diastolic pressure 89 $\pm$ 20 mm. Females in the same age group had a mean value of 157/89 mm. Male subjects aged 82 to 91 years showed an average value of 160/83 mm. A slight rise was observed in the systolic pressure and amplitude with age, and a slight fall in the diastolic pressure.

A detailed study of the diagnosis and therapy of cerebral thrombosis and cerebral hemorrhage was performed by T. Dalsgaard-Nielsen. Among 1000 cases of cerebral vascular accident, hemorrhage was observed in 43 per cent, thrombosis in 50 per cent, and embolism in 7 per cent. The incidence of thrombosis was found to increase with age. The author strongly recommends the use of anticoagulant therapy in cerebral thrombosis in such cases in which the diagnosis is certain.

A. Hjorth and E. Møller-Christensen observed a favorable effect of testosterone propionate administration in elderly women with urinary incontinence. In two-thirds of the patients a 2 to 6 week treatment caused cure or notable improvement of the condition.

The results of two years of rehabilitation activities in De Gamles By were reported by V. Porsman, who emphasized the importance of early referral of elderly invalids to an out-patient geriatric clinic.

Erna Lund and O. Sylvest showed that as a result of the extensive use of antibiotics, particularly penicillin, the incidence of resistant types of staphylococci has increased. In the hospital section of De Gamles By the presence of *Staph. aureus* in the nasal secretion was found in 67 per cent of the patients and in 52 per cent of the staff members, whereas in old persons living outside the hospital the incidence was only 37 per cent. Penicillin resistant types were observed in 54, 37, and 12 per cent, respectively, in the three groups.

In a survey of the socio-medical and socio-psychiatric problems associated with old age, T. Geill emphasized the frequent occurrence of mental disturbances in patients in geriatric departments, including De Gamles By, and discussed the causes for such disturbances. A high incidence of acute confusion is seen in subjects with heart disease and renal disease. Such patients constitute the majority of the geriatric hospital population. The necessity for early and causal treatment of the psychiatric conditions was stressed and the possibility of prophylactic therapy discussed. A closer cooperation between internists and psychiatrists was recommended, and it was suggested that the establishment of geronto-psychiatric hospital units be considered.

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GERONTOLOGIC ACTIVITIES IN AUSTRALIA

O. WESTCOTT FREWIN

In Australia generally there is evidence of a widening consciousness of the problems of gerontology, as manifested by activity in clinical, social, and research spheres.

Geriatrics received a great stimulus by the visit of Dr. J. H. Sheldon, President of the International Association of Gerontology. In his capacity as the 1956 official overseas visitor for the Australian Post-Graduate Federation in Medicine, he lectured in each state of the Commonwealth, his lectures dealing with medical problems of old age and such allied subjects as obesity, appetite, and the collagen diseases.

The Hospital and Charities Commission of Victoria are handling the problems of gerontology in a very realistic way. Since taking office in 1953 the Commission has reviewed the whole question of non-residential as well as residential accommodation for the aged. It has contacted every municipality in the state which sought its cooperation, and as a result many committees have been established and have embarked on programs for clubs, meals on wheels, hostels, flatettes, cottages, and infirmary accommodation.

The Commission's estimate is that with proper attention some 75 per cent of old people who would otherwise become infirm can lead happy, useful, and active lives. Since there were few persons qualified and experienced in the care of old people, philanthropists were persuaded to set up 3 scholarships for medical graduates to spend 12 months abroad studying the latest methods. These men will then return to take up important positions in charge of geriatric units. The Commission also conducted a Geriatrics Conference with 12 lectures being delivered over a period of 6 weeks.

Unlike the method in Great Britain where the Geriatric Unit is actually in the grounds of the General Hospital, the method in Melbourne is to build the Geriatric Unit at one of the homes for the aged. At Mount Royal on the outskirts of Melbourne an entirely new structure has been erected at a cost of £1¼M. This unit incorporates all the latest designs and is well equipped with medical treatment rooms, physiotherapy rooms, and a chiropody room. A fulltime Geriatrician, who is at present overseas studying geriatrics under one of the scholarships mentioned previously, has been appointed to take charge.

The Committee at Mount Royal believes that the main purpose of this unit should be the active short term treatment of those handicapped by age or disease with a view of rehabilitating them as reasonably active, self-supporting members of the community and so enabling them to feed, clothe, wash themselves, and move about unaided. It is proposed that in the future this unit will be the center for the coordination and integration of all geriatric services in the metropolitan area and that its purpose shall include education and indoctrination of medical, nursing, and ancillary workers in geriatrics. A further purpose of the unit will be to provide facilities for gerontologic research. Mount Royal is, as far as Australia is concerned, in the forefront in developing the geriatric services that have been found so effective in alleviating some of the problems of the aged and chronic sick in overseas countries.

In another center a 300-bed tuberculosis sanitorium has recently been converted for geriatric use. This is an interesting commentary on present trends in Public Health inasmuch as the sanitorium, the State's chief center for treatment of tuberculosis, which only a few years ago had a long waiting list, is now handed over in its entirety for the care and treatment of the aged, as well as for research into the special difficulties of the elderly.

A social survey of the older people in Melbourne has been completed by Dr. Bertram Hutchinson of Melbourne University. He has published his findings in a book which presents vividly the situation of aging people in this country. Besides commenting on the old-fashioned and inefficient buildings in which so many of the old people live, Dr. Hutchinson noted a "terrifying atmosphere of boredom" among the elderly because of the lack of anything to do. He reveals a situation so critical that it calls for the combined efforts of all citizens, all religious and philanthropic bodies, and all governments and authorities to help the older person become useful, secure, and happy. Dr. Hutchinson considers that all the beneficient plans that have been de-

vised to improve the lot of the aged have done nothing to change the basic social status of this group—all they have done has been to soften the impact of a system whose attitude it is not proposed to change.

Another social survey is being conducted by the Department of Psychology of the University of Western Australia. This survey, which was started in 1955, is expected to be finished shortly, and the reports will then be compiled into a book. The plan consists of first a statistical study of older people in Western Australia, then an interview conducted among a sample of older people, and finally questionnaire and interview inquiries into the attitude of other age groups toward older people and their problems. The Clinical Research Unit of the Royal Perth Hospital is cooperating with the University in this survey.

Shelter and accommodation of the dependent aged have become largely the responsibility of various denominational bodies, which in most states receive financial assistance from the state government. In many of the homes so constituted the inmates when sick have to be transferred to and cared for in government hospitals, but an increasing number of homes are extending their services so that the old people are looked after while in health and nursed when sick. In Queensland a special Catholic hospital which will accommodate 150 people is being erected for aged incurables. The State Government in Queensland has been very conscious of its responsibilities toward its aged citizens and the state is now in a very satisfactory position, having three homes for the aged directly under the control of the Department of Health and Home Affairs. In all, these homes accommodate 1560 old people and further homes have been planned.

There is quite an amount of gerontologic research being conducted in Australia. In Hobart lipid metabolism is being studied; in Adelaide several aspects of arteriosclerosis are being investigated, and in Perth the Clinical Research Unit, although not actually designated a Geriatric Unit, finds that two-thirds of its patients are over 60, and thus it is expected that some considerable contribution to the knowledge of how to handle the clinical problems of old age will result from their work. Most universities and general hospitals have active research programs.

GERONTOLOGIC AND GERIATRIC ACTIVITIES IN THE ARGENTINE REPUBLIC

MIGUEL C. LASCALEA

Interest in the medical and social problems of old age has increased since the last report given on gerontologic and geriatric activities in this country (*J. Gerontol.* 8: 503-504, 1953). This growing interest has been fundamentally encouraged by the Argentine Society of Gerontology and Geriatrics, which is a center for the principal activities in this field of medicine. As mentioned in the previous report basic research in the Argentine is less general than applied science and for this reason we speak of advancement in both gerontology and geriatrics, since it is difficult to separate the two.

There are three principal medical centers of geriatric-gerontologic investigations, in the Argentine, the Geriatric Service of the Central Military Hospital, El Instituto de Semiología del Hospital Nacional de Clínicas. and the Institute of Oncology "Angel H. Roffo," all of them in Buenos Aires. Geriatrics is practiced and gerontologic studies performed in other medical centers but they constitute individual efforts or episodes without any definite organization and system.

The Service of Geriatrics of the Central Military Hospital, which is under the supervision of the author, is composed of an Out-Patient Department, a hospital department with beds in the general medical service, and a laboratory for gerontologic investigations. Some of the studies performed in this service are: Treatment of arterial hypertension of old age with the combination rauwolfia-apresoline, hemolytic anemias and splenectomy in old age, hepatoptosis, gastroduodenal ulcer in senility.

Research on plasma proteins and lipoproteins in normal and pathologic conditions have been performed in the laboratory of this service since the beginning of the present year, using paper electrophoresis. The investigation relative to normal old age and arterial hypertension of old people have been completed, and the patterns of total and fractioned proteins and lipoproteins in young people, adults, and normal old people have been established. A study of blood electrolytes in normal and pathologic conditions and an investigation of the clinical-chemical alterations in the fractures of neck of femur and the biochemical study in the pre- and post-operative course of patients of advanced age have been started. This latter study includes an investigation of cardiovascular, respiratory, renal, suprarenal and hepatic functions, state of the electrolytes and of the blood proteins (electrophoresis). Next year we expect to explore the renal circulation as related to aging.

In el Instituto de Semiología del Hospital de Clínicas (Director, Professor Tiburcio Padilla) Professor O. Fustinoni is in charge of the clinical investigation, principally in the cardiovascular section.

Some of the papers published are: Bacterial endocarditis in old people, and ballistocardiogram in old age (Drs. O. Fustinoni, J. A. Berreta and H. Mosso); blood pressure in 500 aged patients (Dr. V. R. Mistello); aneurism dissecans of the aorta in geriatrics (Drs. O. Fustinoni and I. Corsini); blood lipids in arteriosclerosis and arterial hypertension of old people have also been studied (Drs. E. H. Mosso and S. Kaplan).

At the Institute of Oncology "Angel A. Roffo," investigations have been made regarding the clinical and chemical changes related to surgery. Drs. W. Cristiani and J. Rabenko have written papers on hypoproteinemia in the post-operative course of old patients; arterial hypotension and its relation to early hyponatremia in the post-operative stage in the elderly; and the causes of death in old patients who have recently undergone surgery.

The Argentine Society of Gerontology and Geriatrics

continues working intensely, and practically all gerontologic and geriatric research performed in the country is referred to this center. During the period October, 1953 to October, 1956, 61 scientific papers were discussed, some of them being the ones already listed. The following are also worth mentioning: Electric shock in old age (Drs. E. E. Krapf and M. Sbarbi); cardiopathies in old people (Dr. I. Berconsky); presenile encephalosis of Pick (Drs. A. Delmar, A. Mosovich, and E. A. Pedace); gonadohormonal study in old people (Drs. E. Rosemblit, D. Hojman, and M. Schteingart); surgical considerations on meningeal hemorrhages in old people (Dr. R. F. Matera).

During 1954, (November 17-19), under the presidency of the reviewer, the First Meetings of Gerontology and Geriatrics were held. In these meetings, in addition to numerous papers, three principal subjects were considered: Diagnosis and treatment of peripheral vascular disease in old age (Drs. J. Diez, H. H. Fernando, and E. D. Diez); diabetics in old people (Drs. P. B. Landabure and B. Rothman); and medical-social problems of senility (Dr. G. Rodriguez).

Some of the important studies presented at these meetings, from the gerontologic point of view, were: The lengthening of life and some of its social effects (Dr. G. Barral Souto); the problem of senility from the statistical point of view (Dr. P. Bottinelli); some biologic levels at different ages (Dr. J. Froimovich, of Chile); diabetes and renal function (J. Curutchet Ragusin).

That same year a joint meeting with the Argentine Society of Urology was held (December, 1954) on the following subjects: Aging of the kidney (Dr. A. Trabucco); pre- and post-operative metabolic aspects in urologic surgery of old individuals (Dr. E. Fongi); and clinical problems in prostatic surgery (Drs. E. A. Rottjer and L. M. Brea).

In 1955 the reviewer organized a post-graduate course on geriatrics at the Faculty of Medicine of Buenos Aires, based fundamentally on the physiopathologic and clinical aspects of aging of the different systems of the human body.

With the object of spreading interest in gerontology and geriatrics, members of the Argentine Gerontologic and Geriatric Association lectured in the cities of Mar del Plata and San Luis in 1955: In Mar del Plata, Dr. D. Passanante, senile cardiology; Dr. G. A. Berretta, treatment of arterial hypertension in old age; Dr. M. C. Lascalea, aging of the digestive system; and in San Luis, Dr. M. C. Lascalea, physiopathology of the digestive system in old people.

Argentine gerontologists and geriatrists keep in touch scientifically with their colleagues of other nations, this being especially so with specialists in Chile, Peru, Venezuela, and Mexico. A delegation from the Argentine was sent to the Third Congress of the International Association of Gerontology where the members read a paper on gastrointestinal hemorrhages caused by arteriosclerosis (Dr. E. A. Rottjer and M. C. Lascalea) and another on electroencephalic alterations in normal old age (Drs. E. A. Rottjer, M. C. Lascalea, and A. Imbriano). At that meeting the Argentine was incorporated as a member of the Governing Body of the International Association of Gerontology. Our country was specially invited to the recent Panamerican Congress of Gerontology, held in México (September 15-22, 1956), and several papers were read, including: Vaginal cytology in senile women (Dr. G. Terzano, J. M. Mezzadra, and A. Arrighi); aging of the kidney (Dr. A. Trabucco); preventive-social aspects of old age (Drs. C. A. Marchese and J. A. Ganduglia Priovano); surgery in old age (Dr. J. A. Ferreira); and hernia of the diaphragmatic hiatus in old age (Dr. A. Rottjer and M. C. Lascalea).

Geriatria, the official journal of the Argentine Society of Gerontology and Geriatrics continues to be published, although not very regularly because of economic reasons. It is widely read among the professional people of the country and is a source of useful information on problems of the specialty.

This brief description shows that the activity in the field of geriatrics and gerontology in this country is intense and increasing day by day.

Above all, physicians have become conscious of the specific problems involving the elderly patient. Activities in the field of gerontologic research are going ahead at a slightly slower pace but nevertheless steadily. The organization of some of the above mentioned investigation centers as well as those which will undoubtedly appear in the future assure prominence to this important aspect of medicine, biology, and sociology.

GERONTOLOGIC ACTIVITIES IN SWEDEN

STEN ECKERSTRÖM

The Committee appointed by the government in 1952 to investigate the care of the aged in this country has presented a report, *The Care of the Aged*,* which was anticipated with considerable interest and has been commented upon to a large extent, both by the newspapers and the radio. The report is now being studied by a number of authorities before the 1957 Swedish Parliament comes to a decision on the Committee's recommendations regarding means of solving the various economic, social, and medical problems of the aged. The rapidly growing number of people over 65 years of age in Sweden (from 1950 to 1970 the increase is calculated to be from 10.2 to 13.5 per cent of the population) makes it necessary to solve many of the previously unresolved questions within the next few years.

The Committee's opinion on the conditions existing today among the aged is based on interviews involving the living conditions (housing, health, activities, etc.) of a large number of pensioners, the results of which have been treated statistically, thus disclosing many problems. A questionnaire was also sent to all the municipalities and counties in order to obtain further elucidation of the question.

The results of their investigation have led the Committee to propose specific recommendations, such as:

Making it possible for aged people to remain in a modern home of their own or in a flat for old age

* The Swedish Government's Public Investigations 1956:1, The Department of Social Affairs.

pensioners as long as possible, even if the old person is crippled to some extent,

Improving the domestic help activity under a public or communal administration by expanding this activity in order to reduce the institutional care of the aged and thus decrease the burden on the institutions as much as possible,

Providing an occupation or activity for old people in order to prevent isolation and passivity, particularly for the old persons who are not able to follow a trade for one reason or another,

Reorganizing the care of the aged in institutions and at home, both physical and mental by placing geriatric clinics in annexes and homes for the chronically ill in various parts of the country,

Educating physicians and nurses in the care of the aged,

Increasing financial support for geriatric and gerontologic research,

Establishing geriatric-somatic and geriatric-psychiatric clinics in connection with university hospitals and some mental hospitals.

The recommended changes in the care of the aged outlined in the Committee's report will doubtless lead to a considerable improvement of resources in Sweden for the care of the aged and for research into the problems of geriatrics and gerontology and also bring to the attention of the Swedish medical profession this important aspect of medicine.

VOLUME 12, SECTION C JANUARY, 1957 NUMBER 1

INDEX TO CURRENT PERIODICAL LITERATURE

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THE SUBJECT categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus, most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given *(B.A.—Biological Abstracts: P.A.— Psychological Abstracts,* and *P.I.—Population Index).* Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the Years 1900-1933,* 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Branch, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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XI. Reactions of the Body as a Whole

(allergy, anoxia, anesthesia, anthropometry, drugs, exercise, immunity, sleep, and temperature regulation)

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XII. Reproductive System

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